Gupta SK, Murthy RC, Chandra SV. Neuromelanin in manganese-exposed primates. *Toxicol Lett* 1980; 6:17-20

Haliwell B. Manganese ions, oxidation reactions and the superoxide radical. *Neurotoxicology* 1984; 5(1):113-118

Hassanein M, Ghaleb HA, Haroun EA, Hegazy MR, Khayaal MAH. Chronic manganism: Preliminary observations on glucose tolerance and serum protein. *Brit Indust Med* 1966; 23:67-70

Heilbronn E, Eriksson H, Haggblad J. Neurotoxic effects of manganese: Studies on cell cultures, tissue homogenates and intact animals. *Neurobehav Toxicol Teratol* 1982; 4:655-658

Hurley LS, Keen CL, Baly DL. Manganese deficiency and toxicity: Effects on carbohydrate metabolism in the rat. *Neurotoxicology* 1984; 5:97-104

Iversen SD, Iversen LL. *Behavioral Pharmacology*. New York and Oxford, Oxford University Press, 1975

Kenten RH, Mann PGJ. The oxidation of manganese by peroxidase systems. *Biochem* 1950; 46:67-73a

Kenten RH, Mann PGJ. Manganese oxidation in the pea plant *(Pisum sativum L.)* grown under conditions of manganese toxicity. *Biochem J* 1957; 65:179-185

Lyden A, Larsson BS, Lindquist NG. Melanin affinity of manganese. *Acta Pharmacol et Toxicol* 1984; 55:133-138

Mella H. The experimental production of basal ganglia symptomatology in Macacus rhesus. *Arch Neurol Psychiat* 1924; 11:405-417

Mena I, Marin O, Fuenzalida S, Cotzias GC. Chronic manganese poisoning - clinical picture and manganese turnover. *Neurology* 1967; 17:128-136

Mena I. Manganese. In: *Metals in the Environment*. Waldron HA, ed. Academic Press, 1980; pp 199-220

Muakkassah-Kelly SF, Andresen JW, Shih JC, Hochstein P. Decreased (3-H-) spiperone binding consequent to lipid peroxidation in rat cortical membranes. *Biochem Biophys Res Comm* 1982; 104:1003-1010

Mustafa SJ, Chandra SV. Levels of 5-hydroxytryptamine, dopamine and norepinephrine in while brain of rabbits in chronic manganese toxicity. *J Neurochem* 1971; 18:931-933

Neff NH, Barrett RE, Costa E. Selective depletion of caudate nucleus dopamine and serotonin during chronic manganese dioxide administration to squirrel monkeys. *Experientia* 1969; 25:1140-1141

Pastuskzoko A, Gordon-Majszak W, Dabrowiecki Z. Dopamine uptake in striatal synaptosomes exposed to peroxidation *in vitro*. *Biochem Pharmacol* 1983; 32:141-146

Pentschew A, Ebner FF, Kovatch RM. Experimental manganese encephalopathy in monkeys - A preliminary report. *J Neuropathol Exp Neurol* 22:488-499

Rodier J. Manganese poisoning in Moroccan miners. *Brit J Ind Med* 1955; 12:21-35

Sadee W, Pfeiffer A, Herz A. Opiate receptor: Multiple effects of metal ions. *J Neurochem* 1982; 39:659-667

Seelert H. Monatschr ein fall chronischer manganvergiftung. *P Psychr U Neurol* 1913; 24:82-92

Usdin TB, Creese I, Snyder SH. Regulation by cations of (3-H)-spiroperidol binding associated with dopamine receptors of rat brain. *J Neurochem* 34:669-676

Van Bogaert L, Dallemagne MJ. Approaches experimentales des troubles nerveux du manganisme. *Mschr Psychiat Neurol* 1943; 111:60-89

Von Oettingen WF. Manganese: Its distribution, pharmacology and health hazards. *Physiol Rev* 1935; 15:174-201

Yase Y. The pathogenesis of amyotrophic lateral sclerosis. *Lancet* 1972; 2:292-295

# ATTACHMENT C-16

Abbott (1987)

than 15 $\mu$m are unlikely to reach the thoracic (tracheobronchial and alveolar) region. Particles of 10 $\mu$m do not reach the alveoli, but ~35% are deposited tracheobronchially. Alveolar deposition is greatest for particles in the 2–4 $\mu$m range and although nearly all particles smaller than 2 $\mu$m reach the alveoli, many remain suspended and are exhaled. All particles < 2 $\mu$m can be conservatively considered to be deposited in the alveoli (U.S. EPA, 1984). Moore et al. (1975) has estimated the size of $Mn_3O_4$ particles from combustion of petrol containing MMT to be ~0.26 $\mu$m and therefore capable of alveolar deposition. While the rate of lung absorption of inhaled Mn in both animals and humans is unknown, the U.S. Task Group on Metal Accumulation (1973) considered only particles less than a few tenths of a micrometre in diameter to be eventually absorbed into the blood. If all the inhaled $Mn_3O_4$ were absorbed, even at a point of high traffic density (0.5 $\mu g\,m^{-3}$), the maximum Mn intake would be 10 $\mu$g (assuming an adult breathes 20 $m^3\,day^{-1}$). The actual intake would be less than this given than an unknown fraction of the inhaled particles would be exhaled immediately and another unknown fraction would be removed by mucociliary clearance.

The possibility that Mn oxides may be absorbed differently in the lung to other Mn compounds may have been answered partially by the experiments of Mena et al. (1969). In these experiments, an airborne aqueous solution of either 54-$MnCl_2$ or 54-$MnO_2$ was absorbed (either in the lung, GI tract or both) after inhalation exposure. Excretion rates in the urine were similar for both compounds and the results suggest that 60–70% of the inhaled Mn was eventually swallowed and absorbed via the GI tract.

With regard to oral intake, WHO (1973) has estimated that the daily dietary intake of Mn ranges between 2 and 3 $mg\,day^{-1}$ for adults. Intake for infants is much lower (0.002–0.004 $mg\,kg^{-1}\,day^{-1}$) due to the low concentration of Mn in both breast and cow's milk. U.S. EPA (1984) data on the concentration in drinking water indicates that the level is very low (median level 4 $\mu g\,l^{-1}$) and not a significant source of dietary Mn. Gastrointestinal absorption of Mn in adults is likely to be less than 5% of the total Mn ingested (WHO, 1981). In anaemic subjects, the rate is probably higher, given that the transport mechanism for Mn and Fe are the same (Mena et al., 1974). Clearance from the respiratory tract is an even smaller source of Mn. The U.S. EPA (1984) estimates an average ingestion of 0.00026 $mg\,day^{-1}$ by this route, assuming 100% deposition and clearance at an ambient exposure level of 0.023 $\mu g\,m^{-3}$.

## COMPARISONS WITH LEAD

A number of the toxicological concerns regarding increased airborne levels of $Mn_3O_4$ from the use of MMT appear to have arisen by comparison with the known toxic effects of lead. A major reason why this is an inappropriate analogy is that Mn is already present in the diet and is absorbed via the GI tract at a high level in comparison to the expected level of pulmonary absorption of the Mn oxides. While Mn may be present in a variety of salts and oxides in food

and air, and the relative absorption rates of these forms of Mn may vary, their toxicological effects are considered to be identical following absorption.

Lead, on the other hand, is not a normal or useful component of the diet and its toxic effects are well characterized at low levels of exposure. While blood lead levels are a reasonably good indicator of recent lead exposure, the levels of Mn in blood or urine are an extremely unreliable indicator of recent or long-term exposure due to rapid removal of Mn from the blood stream ($t_{½}$ = 1.5 min). Levels of Mn in blood do not parallel the presence of psychological or neurological symptoms, and display wide individual variation (Roels et al., 1987b). The Mn level in human tissues also has a relatively short half-life (liver, $t_{½}$ = 25 days). No useful comparison, therefore, can be made between blood Mn and Pb levels.

As discussed earlier, comparisons with lead have been useful for estimating expected airborne levels of Mn resulting from the use of MMT. A further comparison might also be useful for determining the likely route of intake of Mn following exposure to $Mn_3O_4$. Lead-containing particles from car exhausts are absorbed by inhalation or by the ingestion of dust particles on food or other objects in the environment. For children, in particular, the ingestion route is the most significant and the inhalation route is considered a minor exposure pathway. Hence the high blood lead levels found in children living near areas of high traffic density (U.S. DHHS, 1985). Since there is already a high dietary intake of Mn in both children and adults, the contribution from $Mn_3O_4$-containing dust will not significantly increase Mn intake.

## PULMONARY TOXICITY

Inhaled metallic particles can be considered to have one of three fates (Adkins et al., 1980): (i) removal from the lung by exhaled air, by mucociliary mechanisms, by engulfment by pulmonary macrophages, or by lymphatic clearance; (ii) deposited in the lung tissue over a long period with little or no harm; (iii) passage into the systemic circulation. The fate of a particular particle will depend to a large extent on its size, and inhaled Mn particles are expected to be cleared by several of the above mechanisms.

Occupational exposure to Mn dust leading to a high rate of pneumonia has been studied in a large number of epidemiological surveys (see U.S. EPA, 1984). Exposure to high levels of Mn is associated with a syndrome known as 'manganese pneumonia'. The levels required to observe symptoms are generally $> 5\,mg\,m^{-3}$, which is the present limit in the United States for occupational exposure. However, exposure/response relationships are limited by the variable exposure conditions and the number of measurable end points. One study (Nogawa et al., 1973), conducted with Japanese schoolchildren whose school was close to a ferromanganese plant, found there was an increased prevalence of respiratory symptoms (e.g. sputum, wheezing and sore throat) at particularly low exposure levels (3–11 $\mu g\,m^{-3}$). No other study has confirmed these results at such low exposure levels.

capacity and hand tremor. The authors estimate that a time-weighted average exposure to airborne Mn dust of $\sim 1\,mg\,m^{-3}$ over a number of years may lead to the occurrence of pre-clinical signs of intoxication.

## OTHER CHRONIC TOXICITY

Two other possible areas of Mn toxicity have been considered, namely oncogenicity and reproductive effects. Given the relatively low intake of Mn into the bloodstream after airborne $Mn_3O_4$ exposure, an oncogenicity study by the inhalation route could only be useful for the detection of lung tumours. Since there has been no reported increased incidence of lung tumours among occupationally exposed individuals, often at very high doses (see WHO, 1981), the likelihood of Mn being a lung carcinogen seems small. In a paper by Stenback and Rowland (1979), intratracheal instillation of $MnO_2$ dust (1.5 mg once a week for 20 weeks) into hamsters did not increase the incidence of lung tumours and nor did it enhance the level of tumours produced by concurrent instillation of benzo[a]pyrene.

Interest in the possible effects of Mn on reproductive parameters in males has centred around reports by manganese workers of impaired sexual behaviour in the form of diminished libido and impotence. Animal experiments have thus concentrated on morphological and biochemical changes in testes. In the experiments of Chandra et al. (1971, 1973) degenerative changes in semeniferous tubules were observed after 150 days of intraperitoneal administration of $MnCl_2$ at a dose of $8\,mg\,kg^{-1}\,day^{-1}$. Other studies have not been in agreement with the Chandra results, and no definite effects of Mn after oral or inhalation exposure can be identified. The only animal study performed with $Mn_3O_4$ is that by Laskey et al. (1982). Serum testosterone levels and epididymal sperm counts were depressed at dose levels $> 35\,mg\,kg^{-1}$, which are well above the likely human exposure dose level.

In an epidemiological study by Lauwerys et al. (1985), the number of children fathered by workers exposed to a median Mn concentration of $0.97\,mg\,m^{-3}$ was significantly lower than the expected number. This level of exposure is approximately 3–4 orders of magnitude higher than the Mn exposure level likely to arise from the use of MMT.

## CONCLUSIONS

Potential toxicological effects of increased airborne Mn appear to be restricted to the pulmonary and central nervous systems. Effects in the lung such as inflammation, pneumonia and bronchitis are clearly evident in both animals and humans exposed to relatively high levels of Mn, however individual susceptibility and toxic manifestations seems to vary greatly, even after very long exposure periods. Further low level chronic exposure experiments in animals may be necessary to define a no-effect level, particularly with regard to ventilatory performance, which appears to be one of the most sensitive indicators

of lung damage. Further studies are also necessary to measure possible changes in susceptibility to respiratory infection after low-level chronic exposure. The data available at present, however, indicate that the increased level of airborne Mn in the form of $Mn_3O_4$ generated by the combustion of MMT would be approximately three orders of magnitude lower than the level necessary to produce adverse effects in the lung.

Similarly with regard to CNS effects, both animal and human studies to date suggest that relatively high levels of Mn intake are required to produce symptoms of toxicity. In humans, the long time periods required to produce symptoms suggest a cumulative effect. Further research into the mechanism of Mn-initiated CNS effects may lead to a better understanding of dose–response relationships.

On the basis of present information, there is no toxicological evidence to suggest that the increased level of airborne Mn resulting from the combustion of MMT as a petrol additive is likely to constitute a health risk to the general population.

## REFERENCES


Adkins, B., G. Luginbuhl and D. Gardner, 1980. Acute exposure of laboratory mice to manganese oxide. Am. Ind. Hyg. Assoc., J., 41: 495–500.

Bird, E., A. Anton and B. Bullock, 1984. The effect of manganese inhalation on basal ganglia dopamine concentrations in Rhesus monkeys. Neurotoxicology, 5: 59–66.

Canadian Health and Welfare, 1978. Methylcyclopentadienyl manganese tricarbonyl (MMT): An assessment of the human health implications of its use as a gasoline additive. Canadian Health and Welfare, Ottawa.

Chandra, S.V., 1971. Cellular changes induced by manganese in the rat testis. Acta Pharmacol. Toxicol., 29: 75–80.

Chandra, S.V., R. Ara, N. Nagar and P.K. Seth, 1973. Sterility in experimental manganese toxicity. Acta Biol. Med. Ger., 30: 857–862.

Coe, M., R. Cruz and J. van Loan, 1980. Determination of MMT by gas chromatography atomic absorption spectroscopy at ng/m$^3$ levels in air samples. Anal. Chem. Acta, 120: 171–176.

Cooper, W., 1984. The health implications of increased manganese in the environment resulting from the combustion of fuel additives: A review of the literature. J. Toxicol. Environ. Health, 14: 24–46.

Coulston, F. and T. Griffin, 1976. Inhalation toxicology of airborne particulate manganese in Rhesus monkeys. EPA Contract 68-02-0710 Inst. Comp. Human Toxicol. and Int. Centre Environ. Safety, Albany Medical College NY, and Holloman Air Force Base, New Mexico.

Faggan, J., 1975. Letter to the Editor. Environ. Health Perspect., 10: xi–xiv.

Gianutsos, G. and M. Murray, 1982. Alterations in brain dopamine and GABA following inorganic or organic manganese administration. Neurotoxicology, 3: 75–82.

Goodman, H.S., B. Noller, G. Pearman and H. Bloom, 1976. The heavy metal composition of atmospheric particulates in Hobart, Tasmania. Clear Air, 10: 38.

Laskey, J., G. Rehnberg, J. Hein and S. Carter, 1982. Effects of chronic manganese ($Mn_3O_4$) exposure on selected reproductive parameters in rats. J. Toxicol. Environ. Health, 9: 677–687.

Lauwerys, R., H. Roels, P. Genet, G. Toussaint, A. Bouckaert and S. De Cooman, 1985. Fertility of male workers exposed to mercury vapour or to manganese dust: A questionnaire study. Am. J. Ind. Med., 7: 171–176.

Mena, I., K. Horiuchi, K. Burke and A. Cotzias, 1969. Chronic manganese poisoning: Individual susceptibility and absorption of iron. Neurology, 19: 1000–1006.

Mena, I., K. Huriuchi and G. Lopex, 1974. Factors enhancing entrance of manganese into the brain: Iron deficiency and age. J. Nucl. Med., 15: 516–520.

Moore, W., D. Hysell, R. Miller, M. Malanchuk, R. Hinners, Y. Yong and J. Stara, 1975. Exposure of laboratory animals to atmospheric manganese from automotive emissions. Environ. Res., 9: 274–284.

Nogawa, K., E. Kobayashi, M. Sakamoto, M. Fukushima, A. Ishizaki, S. Kagamimori, T. Makino, Y. Hiramaru, S. Kawano, T. Kato, K. Kanagawa and S. Aziami, 1973. Epidemiological studies on disturbance of respiratory system caused by manganese air pollution. Report 1: Effects on respiratory system of junior high school students. Jpn. J. Public Health, 20: 315–326.

Roberts, D., J. Milne, D. Jones, R. Cosstick and D. Williams, 1983. The chemical composition of Sydney brown haze. In: J. Carras and Johnson (Eds), The Urban Atmosphere—Sydney, A Case Study. CSIRO, Melbourne, Australia.

Roels, H., R. Lauwerys, J-P Buchet, P. Genet, M. Sarhan, I. Hanotiau., M de Fays, A. Bernard and D. Stanescu, 1987a. Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system and some biological indices. Am. J. Ind. Med., 11: 307–329.

Roels, H., R. Lauwerys, P. Genet, M.J. Sarhan, M. de Fays, I. Hanotiau and J.P. Buchet, 1987b. Relationship between external and internal parameters of exposure to manganese in workers from a manganese oxide and salt producing plant. Am. J. Ind. Med., 11: 297–307.

Stenback, F. and J. Rowland, 1979. Experimental respiratory carcinogenesis in hamsters: Environmental, physiochemical and biological aspects. Oncology, 36: 63–71.

Ter Haar, G. M. Griffing, M. Brandt, D. Oberding and M. Kapron, 1975. MMT as an antiknock: Composition and fate of manganese exhaust products. Air Pollut. Control Assoc., J., 25: 858.

Ulrich, C., W. Rinehart and W. Busey, 1979a. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol—1. Introduction, experimental design and aerosol generation methods. Am. Ind. Hyg. Assoc., J., 40: 238–244.

Ulrich, C., W. Rinehart, W. Busey and M. Dorato, 1979b. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol II—Clinical observations, haematology, clinical chemistry and histopathology. Am. Ind. Hyg. Assoc., J., 40: 322–329.

Ulrich, C., W. Rinehart and M. Brandt, 1979c. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol III—Pulmonary function, electromyograms, limb tremor and tissue manganese data. Am. Ind. Hyg. Assoc. J., 40: 349–353.

U.S. DHHS (Department of Health and Human Services), 1985. Preventing lead poisoning in young children. Centers for Disease Control, Atlanta.

U.S. EPA, 1984. Health assessment document for manganese. Environmental Criteria and Assessment Office, Cincinnati.

U.S. Task Group on Metal Accumulation, 1973. Accumulation of toxic metals with special reference to their absorption, excretion, and biological half-life. Environ. Physiol. Biochem., 3: 65–107.

WHO (World Health Organisation), 1973. Technical Report Series No: 523. Trace elements in human nutrition. Report of WHO Expert Committee, p. 34.

WHO (World Health Organization), 1981. Manganese. Environ. Health Criteria, 17.

# ATTACHMENT C-17

Cooper (1984)

# THE HEALTH IMPLICATIONS OF INCREASED MANGANESE IN THE ENVIRONMENT RESULTING FROM THE COMBUSTION OF FUEL ADDITIVES: A REVIEW OF THE LITERATURE

W. Clark Cooper

Occupational Health Consultant,
Berkeley, California

*Methylcyclopentadienyl manganese tricarbonyl (MMT) is effective in raising the octane level of gasoline and is currently used in Canada for that purpose in a maximal concentration of 18 mg Mn/l (slightly less than 0.07 g Mn/U.S. gal). It has been estimated that if MMT were used in all U.S. gasoline in these amounts, the median increase of Mn in ambient air would be not more than 0.05 μg Mn/m³, with increments generally less than 0.5 μg Mn/m³ along urban corridors. The scientific literature was reviewed to determine how the increases in environmental manganese predicted from MMT use would relate to the amounts in the natural environment and necessary to life and to the concentrations associated with toxic effects.*

*Even with additional manganese from the use of fuel additives, total Mn intakes would remain within the range of average amounts absorbed from food and water. Respirable manganese in ambient air due to MMT combustion would be many order of magnitude below the concentrations associated with occupational manganism and respiratory problems and also below those reported in isolated episodes of respiratory symptoms in communities near ferromanganese plants.*

*Evidence was reviewed on the possibilities of: (1) increased absorption of inhaled manganese compared with ingested manganese; (2) hypersusceptibility of infants and persons of advanced age; and (3) increased absorption associated with iron deficiency. While relevant to high levels of exposure, these factors would not be expected to lead to toxic effects from the very low concentrations of Mn resulting from MMT use.*

*Experimental animals that inhaled the combustion products of MMT in concentrations of approximately 10, 100, and 1000 μg Mn/m³ for 9 mo did not show toxic effects, although there was temporary elevation of tissue levels of Mn. Rhesus monkeys, susceptible to the neurologic effects of Mn, showed no symptoms after inhaling the combustion products of MMT in concentrations of 100 μg Mn/m³ for up to 66 wk. Monkeys exposed to 5000 μg Mn/m³ also showed no symptoms.*

*There is thus a wide margin of safety between the intakes of Mn essential to health and the high concentrations that have been associated with toxic effects. The small amounts of manganese added to the environment by the combustion of MMT used as a fuel additive would be comparable to the normal background and should not create health problems.*

This report was prepared at the request of the Ethyl Corporation, which asked for an objective review of all pertinent data. Thanks are extended to Mr. C. A. Hall and Dr. Gary Ter Haar of that corporation for their assistance in providing reference material and to Barbara Walker and Barbara Speed for their invaluable help in completing the manuscript.

Requests for reprints should be sent to W. Clark Cooper, M.D., 2150 Shattuck Avenue, Suite 501, Berkeley, California 94704.



Journal of Toxicology and Environmental Health, 14:23–46, 1984

## INTRODUCTION

With continued interest in the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive, it is timely to review the evidence bearing on the possibility of effects on human health from its combustion products. This review updates a report prepared in June 1977 dealing with the use of MMT in unleaded gasoline in the United States (Cooper, 1977). At that time it was concluded that the slight increase in airborne manganese that would result from widespread use of MMT would be within the range of normal manganese intake and should not have any effect on health.

There have been a number of comprehensive reviews of manganese toxicity in recent years (Schroeder, 1970; National Academy of Sciences, 1973; U.S. Environmental Protection Agency, 1975; Matrone et al., 1977; Stokinger, 1981; World Health Organization, 1981). There will be no attempt to duplicate these reviews. Instead, this report is addressed to several key questions relevant to possible harmful effects of MMT combustion products:

1. How would the increments in manganese intake predicted from MMT use relate quantitatively to normal background levels and to levels known to be toxic?
2. Are there differences in the absorption, distribution, and excretion of *inhaled* manganese, as contrasted with *ingested* manganese, which would make small increases in airborne manganese unusually hazardous?
3. Would individuals with iron-deficiency anemias be unusually susceptible because of increased absorption of Mn?
4. Are infants hypersusceptible, because of increased intestinal absorption and poorly developed blood-brain barriers to metals?
5. Are there effects, other than those on the central nervous system associated with high concentrations of Mn, that deserve consideration? These include acute respiratory disease, interference with hematopoiesis, reproductive problems, mutagenicity, and carcinogenicity.
6. From consideration of all the above factors, is the use of MMT as a fuel additive acceptable in terms of the public's health?

## THE USE OF MMT AS A FUEL ADDITIVE

MMT (Fig. 1) in relatively low concentrations has proven to be effective in raising the octane level of gasoline. It is also used in limited quantities as an additive to fuel oils. It is widely used in unleaded gasoline in Canada and on top of lead in some U.S. gasolines.

MMT is a highly toxic compound (Hysell et al., 1974; Stokinger, 1981), and stringent hygenic precautions are essential during its manufacture and handling prior to incorporation in gasoline or fuel oil. However, MMT emitted into the atmosphere is photochemically decomposed, with a very

| od | Manganese (wet weight, μg/g) |
|---|---|
| ackage | 4.68 |
| | 0.31 |
| | 0.35 |
| | 1.02 |
| | |
| | 35.09 |
| alted | 6.91 |
| | |
| fresh | 7.77 |
| sh | 0.41 |
| ined | 0.24 |
| | 0.64 |
| , canned | 0.30 |
| | |
| per | 47.48 |
| | 262.86 |
| der | 0.45 |
| ound | 20.65 |
| fusion | 0.85 |
| s | 275.58 |
| on | 6.9 |

150 μg Mn, while a cup

nanganese, low levels can
t in rural areas and cities
rations are usually quite
e (1981) concluded that
vere invariably man-made.
rotection Agency (1975),
ates, half urban and half
ions less than 0.1 μg/m³
of the sites. Urban areas
0.03 to 0.07 μg/m³. In
ns above 0.5 μg/m³ are
5.0 μg/m³ and quarterly
age on record, 8.3 μg/m³,
n study in West Virginia
Sciences, 1973). Ondov

et al. (1982) reported concentrations of Mn in various U.S. cities from 1973 to 1978 ranging from 17 to 170 ng/m³ (i.e., 0.017-0.17 μg/m³).

Ambient air concentrations reported in studies of possible health effects, to be discussed in a later section, cover a wide range of peak and average values. With a few exceptions they are consistent with the concentrations reported by the EPA.

In summary, in the absence of industrial point sources, average airborne manganese levels are usually less than 0.1 μg/m³, a concentration that is a convenient reference point. In many urban areas concentrations between 0.1 and 1.0 μg/m³ can be found, while near ferromanganese operations, concentrations in the range of 1 to 10 μg/m³ have been reported, with occasional peaks above 10 μg/m³.

*The predicted increment from the combustion of MMT.* By analogy with the airborne concentrations of lead which result from the use of tetraethyl lead, Ter Haar et al. (1975) estimated that if all gasoline contained MMT in a concentration of 0.125 g Mn/U.S. gal (33 mg Mn/l), the median increase in airborne manganese in urban sites in the National Air Sampling Network survey would be 0.05 μg/m³. Along urban street corridors and expressways, the authors estimated that manganese concentrations would generally be less than 1 μg/m³, even under the most unfavorable traffic and weather conditions. The lower concentrations of additive now being recommended or used would result in correspondingly decreased increments of Mn. Thus, the 18 mg Mn/l (0.068 g Mn/U.S. gal) now permitted in Canada would lead to an estimated median increase of about 0.025 μg Mn/m³, with values along expressways generally less than 0.5 μg Mn/m³. Pierson et al. (1978), after measuring Mn concentrations in tunnels of the Pennsylvania turnpike in 1975-1977 during a period of MMT use, concluded that the predictions of Ter Haar appeared to be essentially correct.

Joselow et al. (1978) suggested that the use of MMT in Newark, N.J., had resulted in an increase of manganese in soils near major traffic arteries and caused slight increases of blood manganese in school children. These studies were seriously deficient as circumstantial evidence relating manganese concentrations to the use of MMT, the amount of which could only be inferred. The concentrations found in soil samples ranged from 100 to 600 μg/g, in the lower portion of the range naturally found in soils. The concentration in street dust next to a major roadway (330 μg/g) was only slightly higher than that 70 m distant (290 μg/g). Even if the trivial difference were real, it would be impossible to relate it to MMT use as contrasted with natural variations in soils and the Mn coming from rusted metal and the wearing of manganese alloys stirred up by traffic. The evidence adduced from correlations between manganese and lead concentrations in the blood of children did not take into account the positive association between Pb and Mn levels in blood shown by Zielhuis et al. (1978), which did not appear to reflect relative levels of exposure.

*Occupational exposures.* After consideration of the concentrations of manganese now present in ambient air and the very small increases that might result from MMT use, it is instructive to review the levels of occupational exposures, including those known to have been associated with toxic effects.

The current workplace standard set by the Occupational Safety and Health Administration (OSHA) (1981) is 5000 $\mu g/m^3$ as a ceiling value (Table 2). The American Conference of Governmental Industrial Hygienists (ACGIH) had adopted the same ceiling value in 1963 and in its documentation (1980) states its belief that this provides an ample margin of safety for manganese and most inorganic compounds. For manganese tetroxide (as of 1978) and manganese fume (as of 1979), however, they have recommended a thershold limit value (TLV) of 1000 $\mu g$ Mn/$m^3$ as a time-weighted average (TWA), and for the fume, 3000 $\mu g/m^3$ as a short-term exposure limit (STEL). The World Health Organization Study Group (1980) recommended an occupational limit for manganese in air of 300 $\mu g/m^3$. For a number of years this has been the standard in the U.S.S.R.

As shown in Table 3, there have been many documented occupational exposures that averaged in the 1000 to 10,000 $\mu g/m^3$ range over long periods. Some were in the range of 10,000 to 1,000,000 $\mu g/m^3$. In most of these situations there were workers who exhibited serious toxic effects. There are no documented chronic toxic effects as manifested by central nervous system disease or pulmonary diseases associated with exposures below 5000 $\mu g/m^3$ (ACGIH, 1980). In this context, increases in average exposures of 0.025 to 0.1 $\mu g$ Mn/$m^3$ appear trivial.

TABLE 2. Guidelines and Standards for Manganese in the Workplace[a]

| Source | Applicable dates | Guideline or standard |
|---|---|---|
| ACGIH TLV | 1946–1959 | 6000 $\mu g/m^3$ (TWA) |
| | 1960–1962 | 5000 $\mu g/m^3$ (TWA) |
| | 1963– | 5000 $\mu g/m^3$ (Ceiling value) |
| | 1978– | 1000 $\mu g/m^3$ (TWA for Mn tetroxide) |
| | 1979– | 1000 $\mu g/m^3$ (TWA for Mn fume) |
| | | 3000 $\mu g/m^3$ (STEL for Mn fume) |
| OSHA | 1972– | 5000 $\mu g/m^3$ (Ceiling value) |
| WHO | 1980– | 300 $\mu g/m^3$ (TWA) |

[a]Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; OSHA, Occupational Safety and Health Administration; WHO, World Health Organization; TLV, threshold limit value; TWA, time-weighted average; STEL, short-term exposure level.

n of the concentrations
ıe very small increases that
review the levels of occu-
have been associated with

:.Occupational Safety and
μg/m³ as a ceiling value
ıental Industrial Hygienists
1963 and in its documenta-
ın ample margin of safety
For manganese tetroxide
however, they have recom-
Mn/m³ as a time-weighted
as a short-term exposure
tudy Group (1980) recom-
air of 300 μg/m³. For a
U.S.S.R.
documented occupational
0 μg/m³ range over long
1,000,000 μg/m³. In most
bite serious toxic effects.
as manifested by central
ıssociated with exposures
ıtext, increases in average

:e[d]

| Guideline or standard |
|---|
| )0 μg/m³ (TWA) |
| )0 μg/m³ (TWA) |
| )0 μg/m³ (Ceiling value) |
| )0 μg/m³ (TWA for Mn tetroxide) |
| )0 μg/m³ (TWA for Mn fume) |
| )0 μg/m³ (STEL for Mn fume) |
| )0 μg/m³ (Ceiling value) |
| )0 μg/m³ (TWA) |

:al Industrial Hygienists; OSHA, ılth Organization; TLV, threshold level.

TABLE 3. Examples of Levels of Occupational Exposure to Airborne Manganese[a]

| Operation | Range of averages[b] (μg Mn/m³) | Range of peak levels[b] (μg Mn/m³) | References |
|---|---|---|---|
| Ore crushing mill | 10,400–173,000 | – | Flinn et al. (1940) |
| Ore crushing | 62,500–250,000 | – | Ansola et al. (1944) |
| Permanganate manufacture | 300–250,000 | – | Lloyd Davies (1947) |
| Mining, mine #1 | 187,000–926,000 | – | Rodier (1955) |
| Mining, mine #2 | 65,000–814,000 | – | Rodier (1955) |
| Mining, 1954 | 500–16,300 | – | Schuler et al. (1957) |
| Mining, 1955 | 1,800–46,000 | – | Schuler et al. (1957) |
| Ferromanganese production | 2,300–4,700[c] | – | Whitlock et al. (1966) |
| Mn ore processing | 5,030–11,100 | 5,250–31,500 | Tanaka and Lieben (1969) |
| Ferromanganese production | 1,600–8,600 | 4,430–20,130 | Tanaka and Lieben (1969) |
| Dry battery manufacture | 6,800–42,200 | – | Emara et al. (1971) |
| Ferromanganese production | | | |
| Old preparation plant | 27,000–1,122,000 | 52,000–1,750,000 | Smyth et al. (1973) |
| Blast furnace and pig casting[d] | 120–13,300 | 1,900–206,000 | Smyth et al. (1973) |
| Mn processing | 2,100–12,900 | 5,000–61,500 | Smyth et al. (1973) |
| Ferroalloy production | 301–20,440 | – | Šarić et al. (1977) |
| Ferromanganese production (after controls) | | | |
| Blast furnace cast house[d] | 230–820 | 1,100–22,600 | Ruhf (1978) |
| Pig casting | 390–620 | 3,960–5,200 | Ruhf (1978) |
| Mn processing | 390–2,260 | 1,000–24,300 | Ruhf (1978) |

[a]All studies prior to 1978 were associated with evidences of manganese toxicity in some individuals.
[b]Methods of sample collection differ, i.e., thermal precipitation, electrostatic precipitation, millipore filter sampling.
[c]Values later found to be too low.
[d]F = fume.

## RELEVANT ASPECTS OF MANGANESE METABOLISM

*General considerations.* Manganese shares with many other metals the properties of being essential to health and also being toxic in high concentrations. Fundamental to any consideration of possible harmful effects from environmental exposures to manganese is whether or not the manganese intakes are outside an optimal range between deficiency and toxicity. The body has very efficient homeostatic mechanisms, mediated largely through controlled excretion by way of the liver, bile, and intestinal tract, which can maintain Mn balance despite wide variations in daily intake. The latter is largely from food, as will be pointed out later. There is evidence that variable absorption may also be a factor in homeostasis (Abrams et al., 1976).

*Evidence for essentiality.* The evidence for manganese being essential to life has been conclusively demonstrated in several species of lower animals

and plants (National Academy of Sciences, 1973; Mertz, 1981). The specific functions for humans are, however, still poorly defined. One case has been reported by Doisy (1973) in which deficiency was suspected of causing clinical symptoms. He described an instance where a volunteer in an experiment was given a diet in which Mn was inadvertantly omitted. The volunteer developed mild dermatitis, reddening of his hair and beard, nausea, lowered serum cholesterol, and depressed synthesis of glycoproteins, all of which cleared when Mn was provided.

Some of the most striking effects seen in animals on Mn-deficient diets have related to reproduction (Everson et al., 1959; Apgar, 1968; National Academy of Sciences, 1973). Hurley (1981) recently has summarized the evidence that Mn, as well as copper and zinc, is essential for normal prenatal and neonatal development, with deficiencies resulting in a variety of congenital abnormalities.

*Manganese intake.* The safe and adequate dietary allowance of manganese for an adult recommended by the National Academy of Sciences is 2500 to 5000 μg/d (National Academy of Sciences, 1980; Mertz, 1981). A World Health Organization task force has estimated that average daily intakes by adults range from 2000 to 9000 μg (1981). The most widely accepted figures for the estimated average daily intake is 3000 μg, but Schroeder et al. (1966) stated that a more typical intake in the United States at that time was slightly less. They believed that the refining of grains and sugars had resulted in human intakes being at the margin of manganese deficiency. For example, data were quoted to indicate that a change from white flour to whole wheat flour could increase an adult's dietary intake of Mn from 2200 μg to 8500 μg/d.

Most manganese enters the body from the gastrointestinal tract and is derived from food, with water and air contributing only a small fraction. The World Health Organization task force estimated 0.5 to 200 μg absorbed from water and from less than 2 to 10 μg/d from inhalation. The inhalation intake depends largely on whether a population lives near manganese-emitting industries, especially ferromanganese or silicomanganese operations.

Guthrie and Robinson (1977) reported a study of diets in 23 women in New Zealand and concluded that a daily intake of 2700 μg was typical for nonvegetarian Western diets. On the other hand, Wenlock et al. (1979) found that the average British diet provided 4600 μg Mn/d, of which half came from tea and other beverages.

The absorption of ingested manganese in adults has been estimated at from 3 to 10%, with the lower percentage being widely accepted as being applicable to healthy adults (Matrone et al., 1977).

Studies of Mn intake in human neonates and infants have largely been concerned with the possibility of manganese deficiency (Shaw, 1980). Vuori (1978) has reported on Mn in human milk where the average ranged from 4 to 6 μg/l, with a decline from initial values of 5.9 μg/l to about

3; Mertz, 1981). The specific
/ defined. One case has been
:y was suspected of causing
ière a volunteer in an experi-
antly omitted. The volunteer
r and beard, nausea, lowered
glycoproteins, all of which

nimals on Mn-deficient diets
1959; Apgar, 1968; National
ecently has summarized the
is essential for normal pre-
cies resulting in a variety of

dietary allowance of man-
tional Academy of Sciences
:iences, 1980; Mertz, 1981).
:stimated that average daily
:g (1981). The most widely
ily intake is 3000 μg, but
l intake in the United States
at the refining of grains and
t the margin of manganese
indicate that a change from
se an adult's dietary intake

e gastrointestinal tract and
)uting only a small fraction.
:imated 0.5 to 200 μg ab-
) μg/d from inhalation. The
:r a population lives near
anganese or silicomanganese

:udy of diets in 23 women
ake of 2700 μg was typical
ıand, Wenlock et al. (1979)
500 μg Mn/d, of which half

lults has been estimated at
ıg widely accepted as being
).
d infants have largely been
deficiency (Shaw, 1980).
k where the average ranged
alues of 5.9 μg/l to about

4 μg/l before the second month and rising again about the fifth or sixth month after birth of the child.

Reference Man, a hypothetical 70-kg adult of middle age, contains about 12,000 μg manganese in his entire body, the range being 10,000 to 20,000 μg (World Health Organization, 1981). The concentrations in human tissues do not increase with age (Schroeder et al., 1966). This reflects the excellent homeostatic mechanisms, which keep tissue levels relatively constant despite considerable variations in intake.

*Comparison of pulmonary and gastrointestinal absorption.* Mouri (1973) studied manganese absorption in mice that inhaled manganese dioxide dust, in which 96.8% of the particles were less than 3 μm in diameter, in concentrations averaging 8910 μg Mn/m$^3$ and 5550 μg Mn/m$^3$ for 2 h/d for 8 d and 15 d, respectively. In spite of the high concentrations, no changes were observed in the appearance, body weight, or food intake of the animals.

At both levels of inhalation exposure, the concentrations in most tissues or organs were reported as being higher following inhalation than in controls on comparable oral intakes of manganese or in animals that had ingested much higher amounts of manganese. However, the major differences were in the lung and trachea and in the stomach and small intestine, differences that appear consistent with local deposition and the swallowing of inhaled particles. The relatively small differences in the ratios (inhalation/ingestion) of accumulated manganese in the kidney (1.6 and 1.3), pancreas (1.1 and 1.4), spleen (0.6 and 0.8), brain (1.3), bone (0.95), muscle (2.0), and blood (0.9 and 1.1) provide excellent evidence for the ability of the mice to regulate manganese when inhaled, in spite of the massive doses to which they were exposed.

Adult Swiss mice exposed by *inhalation* to 70,000 μg of $MnO_2$ dust/m$^3$ for 35 h/wk for 4-9 mo (Morganti et al., 1982) showed altered behavioral patterns when compared with controls and with animals that had *ingested* comparable amounts of Mn. The effects were relatively minor, however, and were accompanied by more rapid growth and increased numbers of offspring in some exposed groups. The authors suggested that the latter effects might have reflected a suboptimal Mn content in the laboratory diet.

*Retention and distribution of Mn in younger animals.* There is experimental evidence that very young rats show higher absorption of ingested manganese than adults and that the retention in the brain is greater. Mena (1974) says this is of the order of 70%, compared with less than 3% in adults, and Rehnberg et al. (1980, 1981, 1982) concurred in these estimates.

Kostial et al. (1978) have provided convincing experimental evidence to demonstrate the increased absorption of radioactive manganese chloride in young rats. Gastrointestinal absorption was 39.9% in 1-wk-old animals, as compared with 0.4% in 6-wk-old rats on a milk diet and 0.05% in 6-wk-old rats on a standard diet (which contained considerably more manganese).

There was a significant difference in tissue distribution in sucklings and older rats. However, these changes were not reflected in differences in acute toxicity. The LD50 for $MnCl_2$ was essentially the same at 2 wk and at 18 wk, the values in mg/kg being as follows: 2 wk, 804; 3 wk, 1860; 6 wk, 1712; 18 wk, 850; and 54 wk, 619. The authors concluded that while the data did not support the hypothesis of increased sensitivity to metals in the newborn, it was still highly undesirable to create a high body burden in infancy.

The most pertinent recent work on the retention and distribution of ingested manganese in very young animals is that of Cahill et al. (1980). Their studies used $^{54}Mn_3O_4$ and $^{54}MnCl_2$ and showed that the two compounds displayed different retention and distribution patterns. With the chloride, retention at a dosage of 500 μg Mn/rat was 13.4%, contrasted with 1.1% for the oxide. At 25 μg Mn/rat, the percentages retained were approximately the same, 20.1% and 17.9%. The most striking findings reported by Cahill et al. were that at a single oral dosage of 25 μg, retention peaked at 10 d, with 22% retention, and then declined precipitously through d 19. At 24 h after exposure, infant rats had from 2 to 65 times greater brain concentrations than did adolescent or adult rats, and these remained higher even after 25 or 49 d. At low doses, nearly 50% of ingested and retained Mn was in the liver, but at higher doses—e.g., 500 μg/d, the proportion was much less, suggesting to the authors that higher doses overloaded the liver's sequestering power. These studies provide valuable information that leads to the conclusion that a doubling of the average daily intake of Mn in an infant could not be tolerated as well as it would be in an adult after the necessary Mn reserves had been established. However, the increments in Mn intake that would result from MMT use would be only a minute fraction of an average daily intake from food and background Mn in water and air.

Kontur and Fechter (1982) administered $MnCl_2$ to rats in doses of 0, 25, and 50 μg/g via intubation from birth through 21 d. Mn levels in the brain increased twofold to threefold with evidence that excretion began between 14 and 21 d. There were no effects on growth nor any overt behavioral or neurochemical toxicity. They concluded that the neonatal animal is not particularly susceptible to the neurotoxic effects of Mn.

*Susceptibility of older animals.* There are studies to suggest that very old animals also may be unusually sensitive. Thus, Silbergeld (1982) has shown that rats 24-32 mo old showed significantly lower straital dopamine levels than did rats 2-3 mo old, when both groups were given manganese acetate at 5 mg/l in drinking water. As with most other experimental findings of importance in understanding manganese toxicity, levels of exposure were greatly in excess of those relevant to MMT use.

*Retention and absorption in relation to iron intake.* Mena et al. (1974) suggested that individuals with iron-deficiency anemia might be vulnerable because of increased intestinal absorption. The evidence to support this is

limited to feeding studies with large doses of Mn. The order of increase as shown by Mean et al. (1969) was 3% absorption in normal individuals, compared with 7.5% absorption in anemic subjects. Chandra and Tandon (1973) found that rats on iron-deficient diets given 10,000 μg manganese chloride/kg daily for 15 d had higher manganese content in liver, kidney, and testes than those on a normal iron diet. The ratios were 1.3 to 1, 1.4 to 1, and 1.6 to 1, respectively. Rehnberg et al. (1982) have confirmed the foregoing in studies in which rats ingested $Mn_3O_4$ in diets containing 400, 1100, or 3550 μg Mn/g. Iron-deficient diets promoted Mn absorption and tissue accumulation. These findings, although important, do not seem relevant to the addition of a few micrograms of Mn to the several thousand micrograms present in the average diet.

*Absorption and retention of Mn from MMT combustion.* There are several studies in animals that involve the absorption and tissue localization of manganese derived from MMT. Moore et al. (1975) reported the exposure of rats and hamsters 8 h/d for 56 d to automotive emissions containing Mn particulates that had resulted from the use of MMT as an additive. Both irradiated and nonirradiated exposure chambers were used. The amounts of manganese in the air of the chambers were 117 and 131 $\mu g/m^3$, respectively. These concentrations were more than 200 times the predicted increments in airborne Mn predicted along urban street corridors from the use of MMT as a gasoline additive, and over 4000 times the predicted median increases in ambient air concentrations. Tissue concentrations of Mn in the brain and liver were increased in test animals at the end of 24 wk; the concentrations in the brain were $1\frac{1}{2}$ to 2 times those found in control animals. There were no histopathologic changes.

Ulrich et al. (1979a,b,c) described studies in which rats and squirrel monkeys were exposed to inhaled manganese oxide aerosol produced by the combustion of MMT, with average exposure concentrations of 11.6, 112.5, and 1152 $\mu g/m^3$ 21-22h/d, for 9 mo. While concentrations of manganese in liver, kidney, pancreas, spleen, lung, and blood were elevated after 9 mo, when measured 6 mo after exposure ended they were not elevated in any groups. Brain Mn concentrations were not determined.

Coulston and Griffin (1976) exposed rhesus monkeys to a manganese oxide aerosol, also derived from the combustion of MMT, where concentrations were approximately 100 μg $Mn/m^3$ for periods up to 66 wk. They calculated that the diet of the rhesus monkey contained between 4000 and 5000 μg Mn/d and that there was about 100 μg Mn in all the air inhaled by an animal during each day in the chamber. No toxic effects were observed. In animals sacrificed after 12 mo of exposure, there were slight but statistically significant increases in the manganese concentrations in lungs, liver, pancreas, kidney, and heart muscle. Concentrations were also greater in the pallium cortex, basal ganglia, cerebellum, and pons; the degree of difference was about two-fold with the exception of the pons, which had about four times the amount of manganese in the exposed

animals than in the control animals. This study confirmed that prolonged exposure by inhalation for over a year to concentrations of manganese far greater than the peaks predicted for MMT use led to increases in manganese in the brain, but no symptoms appeared.

The same authors also reported that in rats exposed to airborne manganese from MMT combustion, in concentrations of 100 $\mu g/m^3$ for up to 8 wk, there were increased amounts of Mn in the lung and brain, but that these returned to normal levels within 1 wk after cessation of exposure.

In summary, it appears that the most relevant studies bearing on the possibility of increased accumulation of Mn in tissues resulting from the use of MMT are those that have been done with the actual combustion products. Here, even when exposures involved concentrations exceeding by several orders of magnitude any that would occur in heavily travelled urban areas, increased Mn levels in tissues were relatively low and rapidly returned to pretest levels.

## POTENTIAL FOR CENTRAL NERVOUS SYSTEM EFFECTS

*Human experience.* A disease of the central nervous system resembling Parkinsonism is a distinctive manifestation of chronic manganese poisoning. It is a well-recognized occupational disease that has been the subject of many clinical reports and studies (Flinn et al., 1940; Rodier, 1955; Penalver, 1955; Khazan et al., 1956; Schuler et al., 1957; Whitlock et al., 1966; Emara et al., 1971; Smyth et al., 1973; Hine and Pasi, 1975). In none is there convincing evidence that such chronic manganism occurred in anyone whose inhalation exposures had not exceeded 5000 $\mu g/m^3$ over fairly long periods of time.

There are a few questionable reports of chronic manganism with lower exposures. Whitlock et al. (1966) attributed two cases of chronic neurologic disease to exposures of less than 5000 $\mu g/m^3$. However, Tanaka and Leiben (1969) subsequently reported that the average concentrations of Mn in some areas of the plant in question were 11,000 $\mu g/m^3$ with peaks over 30,000 $\mu g/m^3$. Smyth et al. (1973) described 5 cases of chronic manganism in 71 workers in a Pennsylvania steel plant. One had worked in an area with exposures to ferromanganese fumes averaging only 1000 $\mu g$ $Mn/m^3$, which led the authors to hypothesize and unusual hypersusceptibility. A recent report by Chandra et al. (1981) of suspected neurological involvement in welders exposed to 440-2600 $\mu g$ manganese/$m^3$ has insufficient clinical information to justify firm conclusions. One can conclude that in the range of exposure from 1000 to 5000 $\mu g$ $Mn/m^3$, chronic manganism may occur but has not been clearly proven.

Even with high concentrations in the air, not all workers show neuro-

rmed that prolonged
ations of manganese
to increases in man-

xposed to airborne
of 100 $\mu g/m^3$ for
the lung and brain,
k after cessation of

idies bearing on the
s resulting from the
actual combustion
ntrations exceeding
in heavily travelled
ely low and rapidly

s system resembling
anganese poisoning.
e subject of
955; Penalver,
itlock et al., 1966;
, 1975). In none is
occurred in anyone
$m^3$ over fairly long

ganism with lower
of chronic neuro-
wever, Tanaka and
concentrations of
$\mu g/m^3$ with peaks
es of chronic man-
had worked in an
ng only 1000 $\mu g$
sual hypersuscepti-
ected neurological
ganese/$m^3$ has in-
. One can conclude
/$m^3$, chronic man-

orkers show neuro-

logic symptoms or signs. For example, Lloyd-Davies and Harding (1949) studied workers in a plant where exposures ranged as high as 21,600 $\mu g/m^3$ and found that "no case of systemic manganese poisoning was seen in spite of the closest watch" (p. 89).

The American Conference of Governmental Industrial Hygienists (ACGIH) (1980) in its documentation for the threshold limit value (TLV) for manganese dust and manganese compounds concluded that no evidence of adverse effects had been documented for workers exposed to manganese dust in concentrations averaging below 5000 $\mu g$ Mn/$m^3$, a level that it felt afforded a margin of safety. It regarded manganese tetroxide and fume as more hazardous and recommended for them a more restrictive TLV, i.e., 1000 $\mu g$ Mn/$m^3$ as a TWA, with 3000 $\mu g$ Mn/$m^3$ as a short-term exposure level (STEL) for the fume.

There is little information on tissue levels in humans associated with neurologic disease. Analyses that have been reported have not shown any correlations. For example, Flinn et al. (1940) reported an autopsy on an individual with manganism, 7 yr after exposure, which had averaged 73,000 $\mu g$ Mn/$m^3$ air. There were excess amounts of Mn in the lungs but not in other tissues. It has been suggested by Cotzias (1958) that it is the perfusion of the brain during high turnover of Mn, rather than its storage, that is important. This might occur in individuals who have stored large amounts of Mn in their lungs during industrial dust exposures.

In a systematic study of trace metals in human tissue samples, Schroeder et al. (1966) reported excessive Mn concentrations, more than five times the mean for the organ, in the brains of four individuals who did not have increased concentrations in other organs. Several others showed high concentrations with concurrent elevations in other organs. There were no cases of Parkinsonism in this series.

*Studies of central nervous system effects in lower animals.* No satisfactory small-animal models have been developed for studying symptomatic extrapyramidal disease caused by manganese. Mice, rats, and guinea pigs have proved useful, however, for studies of metal deposition and neurochemical effects (Bull, 1977; Chandra et al., 1979a,b, 1980; Deskin et al., 1980a,b; Hietanen et al., 1981; Shukla and Chandra, 1977, 1979, 1981, 1981; Papavasilou et al., 1975; Donaldson et al., 1980; Donaldson and La Bella, 1981; Seth and Chandra, 1981). A number of these studies used weanling rats and provided evidence that neurochemical changes were produced with smaller doses than required for adult animals (Chandra and Shukla, 1978; Deskin et al., 1980a; Kostial et al., 1978; Seth et al., 1977). Although the amounts of manganese administered were relatively large—e.g., 5-20 mg/kg·d—toxic symptoms and signs were not apparent in most studies. Mice, rats, and guinea pigs are not subject to typical extrapyramidal tract disease, presumably because they do not have pigmentation in the substantia nigra. Mild behavioral changes in mice were described

in one study (Chandra et al., 1979a) when pups whose nursing mothers had been given a 5-mg/ml $MnCl_2$ solution (about 30 ml/d) and were later given increased Mn in drinking water after weaning, showed enhanced motor behavior at 60 and 90 d.

Although these studies provide interesting models for studying the influences of Mn on biogenic amines and a variety of neurologically important enzymes, they are only marginally relevant to the toxicity of MMT combustion products because the levels of Mn exposure were greater by orders of magnitude than any increments from the use of MMT.

Primates develop extrapyramidal disease manifestations from Mn and can be used experimentally, as first shown by Mella (1924). As an example, Neff et al. (1969) have shown that squirrel monkeys that received $MnO_2$ by injection in total dosage of 2000 μg developed neurological signs and reductions in caudate dopamine.

Dastur et al. (1969) studied intraperitoneally administered $^{54}Mn$ in rats and concluded that Mn was taken up very slowly by the central nervous system as compared with other organs, but that it was also retained longer. The periods of observation were 34 d. The authors suggest that this avidity of CNS tissue for manganese might be the cause for the vulnerability of the CNS in chronic manganism. This is a plausible hypothesis when dealing with heavily exposed workers, but it is probably not relevant to the addition of a few micrograms of manganese per day in individuals already handling several thousand micrograms. Even though the half-life of Mn is longer in CNS tissue than in most other tissues, there is no buildup with age at levels of intake in the range of the average diet.

*Toxicologic studies of MMT combustion products.* The studies in animals most relevant to the use of MMT have been those of Ulrich et al. (1979a,b,c) and those of Coulston and Griffin (1976), which were mentioned in the section on absorption and tissue accumulation. The former workers reported studies in which rats and squirrel monkeys inhaled manganese oxide aerosol produced by the combustion of Mn, with average exposure concentrations of 11.6, 112.5, and 1152 $\mu g/m^3$ almost continuously for 9 mo, with no apparent adverse effects. Specific tests for neurologic damage were carried out in the monkeys.

Coulston and Griffin (1976) exposed rhesus monkeys to a manganese oxide aerosol, also derived from the combustion of MMT, where concentrations of approximately 100 μg $Mn/m^3$ were maintained for periods up to 66 wk. No adverse effects were observed. The same investigators also exposed two rhesus monkeys to manganese at 5000 $\mu g/m^3$ in an aerosol produced by the combustion of MMT, for 23 h/d for 23 wk. The animals were then observed for an additional 10 mo; there was no evidence of neurotoxicity. The form of manganese inhaled by animals in the latter experiments was largely $Mn_3O_4$.

*Summary of central nervous system effects.* There appears to be an extremely wide margin of safety between the airborne concentrations of

manganese that have been associated with central nervous system disease in humans and experimental animals and those that might be found in ambient air resulting from the use of MMT. Experimental animals of susceptible species, when exposed for long periods of time to manganese-containing aerosols produced by the combustion of MMT, have not shown neurologic changes. The concentrations tested in some experiments were very high compared with average increments predicted if MMT were a widely used fuel additive, i.e., 5000 $\mu g$ Mn/$m^3$ as compared with 0.025 to 0.05 $\mu g/m^3$.

Although manganese is probably more readily absorbed in infants and crosses the blood-brain barrier more readily, all available evidence would indicate that the amounts of Mn added to ambient air by MMT would fall within the range of normal daily absorption and would not cause neurologic effects, even in the most susceptible portion of the population.

## EFFECTS ON THE RESPIRATORY TRACT

*Human occupational exposures.* Acute effects on the lungs, variously described as pneumonia or pneumonitis, have been reported in industrial workers exposed to manganese (Brezina, 1921; Lloyd-Davies and Harding, 1949; Rodier, 1955; Šarić et al., 1974). In these reports, where manganese concentrations were measured, the peaks have ranged from 16,300 $\mu g/m^3$ to 926,000 $\mu g/m^3$, so that these occurrences are really irrelevant to the proposed use of MMT. It is of interest that in many other work situations where Mn concentrations were in the same range, no pulmonary effects were described. This suggests that there is some covariable, possibly an infectious agent, that explains the pneumopathies.

*Human nonoccupational exposures.* Community experience is not clear-cut. The oft-quoted report of Elstad (1939), based on experience between 1924 and 1934 in the Norwegian town of Sauda, provides circumstantial evidence suggesting an association between atmospheric pollution and lobar pneumonia, but it cannot be definitely related to manganese, which was present in concentrations above 64 $\mu g/m^3$. Studies by Povoleri (1949, 1969) in Aosta, Italy, are inconclusive and cannot be used as evidence. Studies from Japan, reported by Nogawa et al. (1973), Kagamimori et al. (1973), and Yoshikawa et al. (1973) have been reviewed. While they suggested that airborne manganese in the range of 4-7 $\mu g/m^3$ resulted in increased respiratory symptoms, pneumonia, or impaired pulmonary function in school children, these reports have serious deficiencies. There is uncertainty as to the actual levels of airborne Mn, the matching of groups socioeconomically, how biasses in questionnaire replies were eliminated (in view of the respondents' concern about the possible harmfulness of air pollution), and how the role of atmospheric factors other than manganese was evaluated. The Environmental Protection Agency concluded that in these studies, the critical level of Mn was "not well identified in a quantitative

sense" (U.S. Environmental Protection Agency, 1975). The brief reports by Suzuki (1970), based on questionnaire surveys, share some of the same deficiencies and are too limited for evaluation.

Šarić et al. (1975) studied acute respiratory disease in the town of Sibenik on the Dalmation coast, comparing the incidence of acute bronchitis, peribronchitis, and pneumonia over a period of 3 yr in three zones at varying distances from a manganese alloy plant. Mean yearly concentrations of manganese in zone (, nearest the plant, ranged from 0.271 to 0.438 $\mu g/m^3$; in zone II, from 0.176 to 0.254 $\mu g/m^3$; and in zone III, 0.051 to 0.070 $\mu g/m^3$. Weekly averages varied widely, with the maximum values for zones I, II, and III being 1.241, 1.323, and 0.251 $\mu g/m^3$, respectively. There was a slightly greater incidence of acute bronchitis and peribronchitis in the two zones nearer the plant, but no difference in the annual incidence of pneumonia. There was not the expected difference between summer and winter rates for pneumonia, and the authors speculated that this might relate to higher Mn concentrations in summer. The authors regarded their findings as tentative, in view of the impossibility of controlling for population density and the absence of information on air pollutants other than manganese and sulfur dioxide.

*Studies in lower animals.* Bergstrom (1977) reviewed the literature on the acute pulmonary toxicity of manganese and described experimental studies in guinea pigs exposed to $MnO_2$ at concentrations of 22,000 $\mu g/m^3$ where 87% of the particles were greater than 3 $\mu m$ in diameter. He found primary inflammation of the bronchi of limited duration, and a significant decrease in bacterial clearance.

There are limited data supporting alteration of resistance to bacterial and viral pneumonia by exposure of mice to $MnO_2$ aerosols in concentrations of 109 $\mu g/m^3$ (Maigetter et al., 1976).

Adkins et al. (1980b) found no significant pulmonary edema in mice exposed by inhalation to $Mn_3O_4$ for 2 h in concentrations of 1837 $\mu g$ $Mn/m^3$ and no mortality in mice exposed for 2 h to $Mn_3O_4$ aerosols ranging from 1583 to 2599 $\mu g$ $Mn/m^3$. However, pulmonary cells in mice exposed to $Mn_3O_4$ in concentrations of 897 $\mu g$ $Mn/m^3$ for 2 h showed biochemical and enzymatic changes consistent with slight impairment of defense mechanisms (1980a).

In none of the major studies involving exposure of animals to manganese oxides derived from MMT—e.g., those of Moore et al. (1975), where concentrations were 117 $\mu g/m^3$ for 56 d; Coulston and Griffin (1976), where concentrations were 100 $\mu g/m^3$ for many months; and Ulrich et al. (1979a, b,c), with concentrations exceeding 1000 $\mu g/m^3$—were any respiratory-tract problems described.

From review of all of the evidence, it appears extremely unlikely that minute increments in airborne manganese even as great as 1 or 2 $\mu g/m^3$ would have any detectable effect on the lungs.

## OTHER POSSIBLE EFFECTS

The cardiovascular, hematopoietic, and reproductive systems have been mentioned in the literature as the sites of possible toxic effects of manganese. Manganese has also been studied for its mutagenic and carcinogenic potential.

Some manganese salts induce a fall in blood pressure in experimental animals (Kobert, 1833; Schroeder and Perry, 1955; Schroeder et al., 1955), ar.. there is one study reporting that groups of heavily exposed workers :splay slightly lower average systolic pressures (Šarić and Hrustic, 1975).

*Hematopoiesis.* Iron and manganese compete for intestinal absorption, and rats fed high concentrations of Mn in their diets and low iron intakes show more evidence of iron deprivation than animals with normal manganese diets (Carter et al., 1980).

*Reproduction.* There are a variety of adverse effects on reproduction associated with manganese deficiency (Everson et al., 1959; Apgar, 1968; National Academy of Sciences, 1973). Very high amounts of manganese, on the other hand, can produce testicular changes, retarded sexual development, and other reproductive effects in rabbits, mice, and rats (Imam and Chandra, 1975; Gray and Laskey, 1980; Laskey et al., 1982).

*Mutagenicity.* High concentrations of Mn are mutagenic in some *in vitro* test systems (Durham and Wyss, 1957; Orgel and Orgel, 1965; Miyaki et al., 1977; Kaplan, 1962; Putrament et al., 1975; Dube and Loeb, 1975), but not in others (Simmon and Ligon, 1977). These effects may reflect interference or competition with other essential metals.

*Carcinogenesis.* The possible role of manganese as a carcinogen has been reviewed by Kazantzis (1981). DiPaolo (1964) reported that 67% of DBA mice developed lymphosarcomas after 18 mo of manganese chloride administration, compared with 24% in controls. Stoner et al. (1976) reported a slight increase in lung tumors in mice given manganous sulfate at 660 mg/kg intraperitoneally over a period of 30 wk. Fürst (1978) found no excess tumors in rats given manganese powder (10 mg × 24 oral doses). There wre also no effects in mice.

Manganese maleate has been reported as inhibiting new growths with both Ehrlich's tumor in the mouse and Gueri's tumor in the rat [Balo and Banga (1957), reported by Cotzias (1958)]. Sunderman (1977) and Sunderman et al. (1975) showed manganese to be an inhibitor of the development of fibrosarcomas produced by nickel subsulfide.

There are no reports to suggest that manganese is a human carcinogen; in fact there are two studies (Majanen and Soini, 1972; Schrauzer et al., 1977) suggesting an inverse relationship between manganese intake and the incidence of some types of cancer.

In summary, with respect to effects on the cardiovascular, hematopoietic, and reproductive systems, there is no evidence to suggest that small increments in environmental manganese from the combustion of

MMT would have any impact on health. The same is true with respect to mutagenic and carcinogenic effects.

## RECAPITULATION

The questions raised in the introduction to this report have been considered in the light of available environmental, experimental, and epidemiologic data, with the following conclusions:

1. The increments in manganese intake in humans resulting from the use of MMT would be within the physiologic range and far below those shown to be toxic.
2. While there are differences in the absorption, distribution, and excretion of manganese that is inhaled as contrasted with manganese that is ingested, the differences are relatively small. Animals that have inhaled manganese derived from the combustion of MMT in concentrations greatly in excess of any that would result from MMT's use as a gasoline have not shown toxic effects.
3. There is moderately increased absorption of Mn associated with iron-deficiency anemias, but this relates to ingested Mn. Any increments in ingested Mn from MMT use would be within the variations that normally occur from differing dietary intakes.
4. Very young experimental animals have increased intestinal absorption of Mn and poorly developed blood-brain barriers to metals. While this suggests that they might be hypersusceptible to central nervous system effects from manganese, the increments of Mn from MMT use would lie within a range to which they are already being exposed, and far below concentrations where such hypersusceptibility would be operative.
5. There is also no evidence to support any discernible impact of minute increments of Mn from MMT on the respiratory tract, the cardiovascular system, hematopoiesis, or reproduction. Neither should mutagenic or carcinogenic effects be anticipated, in view of the fact that total Mn intakes would remain in the physiologic range essential to health.
6. In spite of the fact that there are gaps in our knowledge of the metabolism of manganese and its functions and effects in biologic systems, these are more than balanced by experimental studies with high concentrations of Mn derived from the combustion of MMT. The minute increments of Mn that would result from the use of MMT as a gasoline additive should not have any impact on the public's health.

## REFERENCES

Abrams, E., Lassiter, J., Miller, W. J., Neathery, M. W., Gentry, R. P., and Searth, R. D. 1976. Absorption as a factor in manganese homeostasis. *J. Anim. Sci.* 42:630-636.

Adkins, B. Jr., Luginbuhl, G. H., and Gardner, D. E. 1980a. Biochemical changes in pulmonary cells following manganese oxide inhalation. *J. Toxicol. Environ. Health* 6:445-454.

Adkins, B. Jr., Luginbuhl, G. H., and Gardner, D. E. 1980b. Acute exposure of laboratory mice to manganese oxide. *Am. Ind. Hyg. Assoc. J.* 41:494-500.

American Conference of Governmental Industrial Hygienists, Inc. 1980. *Documentation of the Threshold Limit Values*, fourth ed., pp. 250-251, 253. Cincinnati, Ohio: ACGIH.

Apgar, J. 1968. Effect of zinc deficiency on parturition in the rat. *Am. J. Physiol.* 215:160-163.

Bergstrom, R. 1977. Acute pulmonary toxicity of manganese dioxide. *Scand. J. Work Environ. Health* 3(suppl. 1): 41.

Brezina, E. 1921. *Internationale Ubersicht uber Gewerbekrankheiten nach der Berichten der Gewerbeinspektionen der Kulturlander uber das Jahr 1913*, vol. 8. Berlin: Springer.

Bull, R. J. 1977. Effects of manganese and their modification by hexametaphosphate. EPA Health Effects Research Laboratory Report, NTIS, PB-272-264.

Bull, R. J., and Craun, G. F. 1977. Health effects associated with manganese in drinking water. *J. Am. Water Works Assoc.* 662-663.

Cahill, D. F., Bercegeay, M. S., Haggerty, R. C., Gerding, J. E., and Gray, L. E. 1980. Age-related retention and distribution of ingested $Mn_3O_4$ in the rat. *Toxicol. Appl. Pharmacol.* 53:83-91.

Carter, S. D., Hein, J. F., Rehnberg, G. L., and Laskey, J. W. 1980. Chronic manganese oxide ingestion in rats: Hematological effects. *J. Toxicol. Environ. Health* 6:207-216.

Chandra, S. V., and Shukla, G. S. 1978. Manganese encephalopathy in growing rats. *Environ. Res.* 15:28-37.

Chandra, S. V., and Tandon, S. K. 1973. Enhanced manganese toxicity in iron-deficient rats. *Envrion. Physiol. Biochem.* 3:230-235.

Chandra, S. V., Shukla, G. S., and Saxena, D. K. 1979a. Manganese-induced behavioral dysfunction and its neurochemical mechanism in growing mice. *J. Neurochem.* 33:1217-1221.

Chandra, S. V., Srivastava, R. S., and Shukla, G. S. 1979b. Regional distribution of metals and biogenic amines in the brain of monkeys exposed to manganese. *Toxicol. Lett.* 4:189-192.

Chandra, S. V., Shukla, G. S., Srivastava, R. S., and Gupta, S. K. 1980. Combined effects of metals on biogenic amines and their distribution in the brain of mice. *Arch. Environ. Contam. Toxicol.* 9:79-85.

Chandra, S. V., Shukla, G. S., Srivastava, S., Singh, H., and Gupta, V. P. 1981. An exploratory study of manganese exposure to welders. *Clin. Toxicol.* 18:407-416.

Cooper, W. C. 1977. Airborne manganese and public health. Report by Equitable Environmental Health Inc., Berkeley, Calif., June 14.

Cotzias, G. C. 1958. Manganese in health and disease. *Physiol. Rev.* 38:503-532.

Coulston, F., and Griffin, T. 1976. Inhalation toxicology of airborne particulate manganese in rhesus monkeys. Institute of Comparative and Human Toxicology, International Center of Environmental Safety, Albany Medical College, Holloman Air Force Base, New Mexico. EPA Contract No. 68-02-0710. (Also EPA-600/1-77-026, May 1977.)

Dastur, D. K., Manghani, D. K., Raghavendran, K. V., and Jeejeebhoy, K. V. 1969. Distribution and fate of $Mn^{54}$ in the rat, with special reference to the CNS. *Q. J. Exp. Physiol.* 54:322-331.

Deskin, R., Bursian, S. J., and Edena, F. W. 1980a. Neurochemical alterations induced by manganese chloride in neonatal rats. *Neurotoxicology* 2:65-73.

Deskin, R., Bursian, S. J., and Edena, F. W. 1980b. An investigation into the effects of manganese and other divalent cations on tyrosine hydroxylase activity. *Neurotoxicology* 2:75-81.

DiPaolo, J. A. 1964. The potentiation of lymphosarcomas in mice by manganese chloride. *Fed. Proc.* 23:393.

Doisy, E. A. Jr. 1973. Micronutrient controls on biosynthesis of clotting proteins and cholesterol. In *Trace Substances in Environmental Health-VI*, ed. D. D. Hemphill, pp. 193-199.

Donaldson, J., and LaBella, F. 1982. Control of free radical generation as the basis for physiological and pathological roles of manganese in brain. Presented at International Conference of Neurotoxicology of Selected Chemicals. Lead, Tin, Manganese, Kepone, September 20-24.

Donaldson, J., LaBella, F. S., and Gesser, D. 1980. Enhanced autoxidation of dopamine as a possible basis of manganese neurotoxicity. *Neurotoxicity* 2:53-64.

Dube, D. K., and Loeb, L. A. 1975. Manganese as mutagenic agent during *in vitro* DNA synthesis. *Biochem. Biophys. Res. Commun.* 67:1041-1046.

Durham, N. N., and Wyss, O. 1957. Modified method of determining mutation rates in bacteria. *J. Bacteriol.* 74:548–552.

Elstad, D. 1939. Manganese-containing factory smoke as a predisposing cause in pneumonia epidemics in an industrial district. *Nord. Med.* 3:2527–2533.

Emara, A. M., El-Ghawabi, S. H., Madkour, O. I., and El-Samra, G. H. 1971. Chronic manganese poisoning in the dry battery industry. *Br. J. Ind. Med.* 28:78–82.

Everson, G. J., Hurley, L. S., and Geiger, J. F. 1959. Manganese deficiency in the guinea pig. *J. Nutr.* 68:49–56.

Flinn, R. H., Neal, Reinhart, W. H., Dallavalle, J. M., Fulton, W. B., and Dooley, A. E. 1940. Chronic manganese poisoning in an ore-crushing mill. Federal Security Agency, U.S. Public Health Service. Washington: D.C.: Bulletin 247, U.S. Government Printing Office.

Furst, A. 1978. Tumorigenic effect of an organomanganese compound on F344 rats and Swiss albino mice: Brief communication. *J. Natl. Cancer Inst.* 60:1171–1173.

Gray, L. E. Jr., and Laskey, J. W. 1980. Mutivariate analysis of the effects of manganese on the reproductive physiology and behavior of the male house mouse. *J. Toxicol. Environ. Health* 6:861–867.

Guthrie, B. E., and Robinson, M. F. 1977. Daily intakes of manganese copper, zinc, and cadmium by New Zealand woman. *Brit. J. Nutr.* 38:55–63.

Hietanen, E., Kilpio, J., and Savolainen, H. 1981. Neurochemical and biotransformational enzyme response to manganese exposures in rats. *Arch. Environ. Contam. Toxicol.* 10:339–345.

Hine, C. H., and Pasi, A. 1975. Manganese intoxication. *West. J. Med.* 123:101–107.

Hurley, L. S. 1981. Teratogenic aspects of manganese, zinc, and copper nutrition. *Physiol. Rev.* 61:249–295.

Hysell, D. K., Moore, W. Jr., Stara, J. F., Miller, R., and Campbell, K. I. 1974. Oral toxicity of methylcyclopentadienyl manganese tricarbonyl (MMT) in rats. *Environ. Res.* 7:158–168.

Imam, Z., and Chandra, S. V. 1975. Histochemical alterations in rabbit testis produced by manganese chloride. *Toxicol. Appl. Pharmacol.* 32:534–544.

Ishikawa Prefecture. 1971. White paper on pollution. Ishikawa Prefecture. Pollution & Environment Division, Ishikawa Prefecture Government, Ishikawa Prefecture, Japan (EPA TR-118-75.

Joselow, M. M., Tobias, E., Koehler, R., Coleman, S., Boden, J., and Gause, D. 1978. Manganese pollution in the city environment and its relationship to traffic density. *Am. J. Pub. Health* 68:557–560.

Kagamimori, S., Makino, N., Hiramaru, Y., Kawano, S., Kato, T., Nogawa, K., Kobayashi, E., Sakamoto, N., Fukushima, M., Ishizaki, A., Kanagawa, K., and Azami, S. 1973. Studies concerning the effects on the respiratory organs of atmospheric pollution caused by dusts consisting chiefly of manganese. 2nd report. Concerning the changes in the effects on the human organism when the environment is improved. *J. Jap. Soc. Public Health* 20:413–420.

Kaplan, R. W. 1962. Probleme der prufung von pharmaka, zusatzstoffen u.a. chemikalien auf ihre mutationsauslosende wirkung. *Naturwissenschaften* 49:457–462.

Kazantzis, G. 1981. Role of cobalt, iron, lead, manganese, mercury, platinum, selenium, and titanium in carcinogenesis. *Environ. Health Perspect.* 40:143–161.

Khazan, G. L., Stanislavski, Y. M., Vasilenko, Y. V., Khizhnyakova, L. V., Baranenko, A. A., Kutepov, V. N., Nestrugina, Z. F., Nerubenko, A. B., and Protopopova, V. P. 1956. Working conditions and health status of workers in the Nikopol manganese mines. In *Vrachnebnoye Delo* nos. 1–5, pp. 227–291, *Transl. Natl. Tech. Information Service* PB-262-064-T.

Kobert, R. 1883. Zur pharmakologie des mangan und eisens. *Arch. Exp. Pathol. Pharmakol.* 16:361–392.

Kontur, P., and Fechter, L. 1982. A neurochemical and behavioral study of neonatal manganese exposure. Presented at International Conference of Neurotoxicology of Selected Chemicals. Lead, Tin, Manganese, Kepone. September 20–24.

Kostial, K., Kello, D., Jugo, S., Rabar, I., and Malijkovic, T. 1978. Influence of age on metal metabolism and toxicity. *Environ. Health Perspect.* 25:81–86.

Laskey, J. W., Rehnberg, G. L., Hein, J. F., and Carter, S. D. 1982. Effects of chronic manganese ($MN_3O_4$) exposure on selected reproductive parameters in rats. *J. Toxicol. Environ. Health* 9:677–687.

Lloyd Davies, T. A. 1946. Manganese pneumonitis. *Br. J. Ind. Med.* 3:111-135.

Lloyd Davies, T. A., and Harding, H. E. 1949. Manganese pneumonitis: Further clinical and experimental observations. *Br. J. Ind. Med.* 6:82-90.

Maigetter, R. Z., Ehrlich, R., Fenters, J. D., and Gardner, D. E. 1976. Potentiating effects of manganese dioxide on experimental respiratory infections. *Environ. Res.* 11:386-391.

Majanen, H., and Soini, S. 1972. Possible causal relation between nutritional imbalances, especially manganese deficiency, and susceptibility to cancer in Finland. *Ann. Agric. Fenn* 11:391-406.

Matrone, G., Jenne, E. A., Kubota, J., Mena, I., and Newberne, P. M. 1977. Manganese. In *Geochemistry and the Environment. The relution of Other Selected Trace Elements to Health and Disease*, vol. 2, Chapter 4, pp. 29-39. National Academy of Sciences, Washington, D.C.

Mella, H. 1924. The experimental production of basal ganglion symptomatology in Macacus rhesus. *Arch. Neurol. Psychiatry* 11:405-417.

Mena, I. 1974. The role of manganese in human disease. *Ann. Clin. Lab. Sci.* 4:487-491.

Mena, I., Marin, O., Fuenzalida, S., and Cotzias, G. C. 1967. Chronic manganese poisoning: Clinical picture and manganese turnover. *Neurology* 17:128-136.

Mena, I., Horiuchi, K., Burke, K., and Cotzias, G. C. 1969. Chronic manganese poisoning: Individual susceptibility and absorption of iron. *Neurology* 19:1000-1006.

Mena, I., Horiuchi, K., and Lopez, G. 1974. Factors enhancing entrance of manganese into the brain: Iron deficiency and age. Abstract. *J. Nucl. Med.* 15:516.

Mertz, W. 1981. The essential trace elements. *Science* 213:1322-1338.

Miyaki, M., Murata, I., Osabe, M., and Ono, T. 1977. Effect of metal cations on misincorporation by *E. coil* DNA polymerases. *Biochem. Biophys. Res. Commun.* 77:854-860.

Moore, W., Hysell, D., Miller, R., Malanchuk, M., Hinners, R., Yang, Y., and Stara, J. F. 1975. Exposure of laboratory animals to atmospheric manganese from automotive emissions. *Environ. Res.* 9:274-284.

Morganti, J. B., Lown, B. A., D'Agostino, A., Rosemary, B., Stineman, C. H., and Massaro, E. J. 1982. Uptake, pathology, and behavioral effects of inhalation exposure to manganese ($MnO_2$) in the mouse. Presented at International Conference of Neurotoxicology of Selected Chemicals. Lead, Tin, Manganese, Kepone, September 20-24.

Mouri, T. 1973. Experimental studies on the inhalation of manganese dust. *Shikoku Ishi* 29:118-129.

National Academy of Sciences. 1973. Medical and biologic effects of environmental pollutants—Manganese. A report of the Committee on Biologic Effects of Atmospheric Pollutants. NRC-NAS, Washington, D.C.

National Academy of Sciences. 1980. Recommended dietary allowances. Occupational Safety and Health Administration, National Academy of Sciences, Washington, D.C.

Neff, N. H., Barrett, R. E., and Costa, E. 1969. Selective depletion of caudate nucleus dopamine and serotonin during chronic manganese dioxide administration to squirrel monkeys. *Experientia* 25:1140-1141.

Nogawa, K., Kobayashi, E., Sakamoto, M., Fukushima, N., Ishizaki, A., Makino, N., Kagamimori, S., Hiramaru, Y., Kawano, S., Kato, T., Kanekawa, K., and Shozo. 1973. Studies of the effects on the respiratory organs of air pollution consisting of dusts composedmainly of manganese (first report). *Nippon Koshir Eisei Zusshi (Jap. J. Public Health)* 20:315-325.

Occupational Safety and Health Administration. 1981. OSHA Safety and Health Standards (29 CFR 1910), U.S. Department of Labor, OSHA 2206, Section 1910. 1000, p. 634, RV June.

Ondov, J. M., Zoller, W. H., and Gordon, G. E. 1982. Trace element emissions on aerosols from motor vehicles. *Environ. Sci. Technol.* 16:318-328;

Orgel, A., and Orgel, L. E. 1965. Induction of mutations in bacteriophage T4 with divalent manganese. *J. Mil. Biol.* 14:453-457.

Papavasiliou, P. S., Miller, S. J., Cotzias, G. C., Kraner, H. W., and Hsieh, R. S. 1975. Sequential analysis: Manganese catecholamines and L-dopa induced dyskinesia. *J. Neurochem.* 25:215-219.

Penalver, R. 1955. Manganese poisoning. *Ind. Med. Surg.* 24:1-7.

Perron, W. R., McKee, D. E., Brachaczek, W. W., and Butler, J. W. 1978. Methylcyclopentadienyl manganese tricarbonyl: Effect on manganese emissions from vehicles on the road. *J. Air Pollut. Control Assoc.* 28:692-693.

Povoleri, F. 1949. Bronchopneumonia and the production of ferromanganese. (Abstract.) *J. Ind. Hyg. Toxicol.* 31:79.

Povoleri, F. 1969. Bronchopneumonia and the production of ferromanganese. Prepared for the National Air Pollution Control Administration by the Franklin Institute Research Laboratories. University of Milan, Italy.

Putrament, A., Baranowska, H., Ejchart, A., and Prazmo, W. 1975. Manganese mutagenesis in yeast. A practical application of manganese for the induction of mitochondrial antibiotic resistant to mutations. *J. Gen. Microbiol.* 90(2):265–270.

Rehnberg, G. L., Hein, J. F., Carter, S. D., and Laskey, J. W. 1980. Chronic manganese oxide administration to preweanling rats: manganese accumulation and distribution. *J. Toxicol. Environ. Health* 6:217–226.

Rehnberg, G. L., Hein, J. F., Carter, S. D., Linko, R. S., and Laskey, J. W. 1981. Chronic ingestion of $Mn_3O_4$ by young rats: Tissue accumulation, distribution, and depletion. *J. Toxicol. Environ. Health* 7:263–272.

Rehnberg, G. L., Hein, J. F., Carter, S. D., Linko, R. S., and Laskey, J. W. 1982. Chronic ingestion of $Mn_3O_4$ by rats: Tissue accumulation and distribution of manganese in two generations. *J. Toxicol. Environ. Health* 9:175–188.

Rodier, J. 1955. Manganese poisoning in Moroccan miners. *Br. J. Ind. Med.* 12:21–35.

Ruhf, R. C. 1978. Control of manganese dust and fume exposures at a ferromanganese production and processing facility. *J. Occup. Med.* 20:626–628.

Šarić, M., and Hrustic, O. 1975. Exposure to airborne manganese and arterial blood pressure. *Environ. Res.* 10:314–318.

Šarić, M., Lucić-Palaić, S., Pauković, R., and Holetić, A. 1974. Respiratory effects of manganese (djelovanje mangana Na Respiratorni Sistem). *Arh. Hig. Rada Toksikol.* 25:15–26.

Šarić, M., Ofner, E., and Holetić, A. 1975. Acute respiratory diseases in a manganese contaminated area. Presented at the International Conference on Heavy Metals in the Environment, Toronto, Canada, October.

Šarić, M., Markicevic, A., and Hrustic, O. 1977. Occupational exposure to manganese. *Br. J. Ind. Med.* 34:114–118.

Schrauzer, G. N., White, D. A., and Schneider, C. J. 1977. Cancer mortality correlation studies IV. Associations with dietary intakes and blood levels of certain trace elements, notable SE-antagonists. *Bioinorg. Chem.* 7:35–56.

Schroeder, H. A. 1970. Manganese. Air Quality Monograph 70-17. American Petroleum Institute, Washington, D.C.

Schroeder, H. A., and Perry, H. M. 1955. Antihypertensive effects of metal binding agents. *J. Lab. Clin. Med.* 46:416–422.

Schroeder, H. A., Perry, H. M., Dennis, E. G., and Mahoney, L. E. 1955. Pressor substances in arterial hypertensions. Chemical and pharmacological characteristics of pherentasin. *J. Exp. Med.* 102: 319–333.

Schroeder, H. A., Balassa, J. J., and Tipton, I. H. 1966. Essential trace metals in man: Manganese, a study in homeostatis. *J. Chron. Dis.* 19:545–571.

Schuler, P., Oyanguren, H., Maturana, V., Valenzuela, A., Cruz, E., Plaza, V., Schmidt, E., and Haddad, R. 1957. Manganese poisoning: Environmental and medical study at a Chilean mine. *Ind. Med. Surg.* 26:167–173.

Seth, P. K., and Chandra, S. V. 1982. Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese toxicity. Presented at International Conference of Neurotoxicology of Selected Chemicals. Lead, Tin, Manganese, Kepone, September 20–24.

Seth, P. K., Husain, R., Mushtaq, M., and Chandra, S. V. 1977. Effect of manganese on neonatal rat: Manganese concentration and enzymatic alterations in brain. *Acta Pharmacol. Toxicol.* 40: 553–560.

Shaw, J. C. L. 1980. Trace elements in the fetus and young infant. II. Copper, manganese, selenium and chromium. *Am. J. Dis. Child.* 134:74–81.

Shukla, G. S., and Chandra, S. V. 1977. Levels of sulfhydryls and sulfhydryl-containing enzymes in brain, liver and testis of manganese treated rats. *Arch. Toxicol.* 37:319–325.

manganese. (Abstract.) *J. Ind.*

omanganese. Prepared for the
stitute Research Laboratories.

anganese mutagenesis in yeast.
hondrial antibiotic resistant to

. Chronic manganese oxide ad-
stribution. *J. Toxicol. Environ.*

J. W. 1981. Chronic ingestion
depletion. *J. Toxicol. Environ.*

W. 1982. Chronic ingestion of
anese in two generations. *J.*

*d.* 12:21-35.
a ferromanganese production

erial blood pressure. *Environ.*

iratory effects of manganese
*ol.* 25:15-26.
n a manganese contaminated
the Environment, Toronto,

e to manganese. *Br. J. Ind.*

tality correlation studies IV.
race elements, notable SE-

nerican Petroleum Institute,

netal binding agents. *J. Lab.*

Pressor substances in arterial
rentasin. *J. Exp. Med.* 102:

etals in man: Manganese, a

laza, V., Schmidt, E., and
l study at a Chilean mine.

tter receptors in developing
Conference of Neurotoxi-
er 20-24.
manganese on neonatal rat:
*Pharmacol. Toxicol.* 40:

oper, manganese, selenium

ryl-containing enzymes in
·325.

Shukla, G. S., and Chandra, S. V. 1979. Species variation in manganese induced changes in brain biogenic amines. *Toxicol. Lett.* 3:249-253.

Shukla, G. S., and Chandra, S. V. 1981. Straital dopamine turnover and L-dopa treatment after short-term exposure of rats to manganese. *Arch. Toxicol.* 47:191-196.

Shukla, G. S., and Chandra, S. V. 1982. Current status of striatal catecholamines in manganese poisoning. Presented at International Conference of Neurotoxicology of Selected Chemicals. Lead, Tin, Manganese, Kepone, September 20-24.

Silbergeld, E. K. 1982. Current state of neurotoxicology, basic and applied. *Trends Neurosci.* 5:291-294.

Simmon, V. F., and Ligon, S. L. 1977. *In vitro* microbiological mutagenicity studies of Ethyl Corporation compounds. Stanford Research Institute, Interim Report. SRI, Menlo Park, Calif., February.

Smyth, L. T., Ruhf, R. C., Whitman, N. E., and Dugan, T. 1973. Clinical manganism and exposure to manganese in the production and processing of ferromanganese alloy. *J. Occup. Med.* 15:101-109.

Stokinger, H. E. 1981. The metals: Manganese, Mn. In *Patty's Industrial Hygiene and Toxicology*, third ed., vol. IIA, eds. G. D. Clayton and F. E. Clayton. New York: Wiley.

Stoner, G. D., Shimkin, M. B., Troxell, M. C., Thompson, T. L., and Terry, L. S. 1976. Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res.* 36:1744-1747.

Sunderman, F. W. Jr., Lau, T. J., and Cralley, L. J. 1974. Inhibitory effect of manganese upon muscle tumorigenesis by nickel subsulfide. *Cancer Res.* 34:92-95.

Sunderman, F. W. Jr. 1977. Metal carcinogenesis. *Advances in Modern Toxicology*, vol. 2. *Toxicology of Trace Elements*, eds. R. A. Goyer and M. A. Mehlman, pp. 257-297. Washington, D.C.: Hemisphere.

Sunderman, F. W. Jr., Lau, I. J., Menghetti, P., Onkelin, C., Becker, N., and Goldblatt, P. 1975. Manganese inhibition of nickel carcinogenesis in rats. (Abstract.) *Ann. Clin. Lab. Sci.* 54:316-317.

Suzuki, Y. 1970. Concerning the environmental pollution by manganese. *Ind. Med. (Jap.)* 12:529-533.

Tanaka, S., and Lieben, J. 1969. Manganese poisoning and exposure in Pennsylvania. *Arch. Environ. Health*, 19:674-684.

Ter Haar, G. L., Griffing, M. E., Brandt, M., Oberding, D. G., and Kapron, M. 1975. Methylcyclopentadienyl manganese tricarbonyl as an antiknock: Composition and fate of manganese exhaust products. *J. Air Pollut. Control Assoc.* 25:858-860.

Ulrich, C. E., Rinehart, W., and Busey, W. 1979a. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. I. Introduction, experimental design and aerosol generation methods. *Am. Ind. Hyg. Assoc. J.* 40:238-244.

Ulrich, C. E., Rinehart, W., Busey, W., and Dorato, M. A. 1979b. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. II. Clinical observations, hematology, clinical chemistry and histopathology. *Am. Ind. Hyg. Assoc. J.* 40:322-329.

Ulrich, C. E., Rinehart, W., and Brandt, M. 1979c. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. III. Pulmonary function, electromyograms, limb tremor, and tissue manganese data. *Am. Ind. Hyg. Assoc. J.* 40:349-353.

U.S. Environmental Protection Agency. 1975. Scientific and technical assessment report on manganese. EPA-600/6-74-002. Washington, D.C.: U.S. Government Printing Office.

Vuori, E. 1978. A longitudinal study of manganese in human milk. *Acta Paediatr. Scand.* 68:571-573.

Wenlock, R. W., Buss, D. H., and Dixon, E. J. 1979. Trace nutrients. 2. Manganese in British food. *Br. J. Nutr.* 41:253-261.

Whitlock, C. M. Jr., Amuso, S. J., and Bittenbender, J. B. 1966. Chronic neurological disease in two manganese steel workers. *Am. Ind. Hyg. Assoc. J.* 27:454-459.

World Health Organization Study Group. 1980. Recommended health-based limits in occupational exposure to heavy metals: Report of a WHO Study Group. WHO Technical Report Series No. 647. World Health Organization, Ch-1211 Geneva 27, Switzerland.

World Health Organization. 1981. Environmental Health Criteria 17. Manganese. International Program on Chemical Safety. World Health Organization, Geneva.

Yoshikawa, Z., Kobyashi, E., Sakamoto, M., Fukushima, K., Ishizaki, A., Makino, T., Kyomori, S., Hiramaru, Y., Kawano, S., Kato, T., and Kanagawa, K. 1973. Studies on the effects to respirators by atmospheric dust contaminants principally in the form of manganese. *Nippon Koshu Eisei Zasshi* 20: 315-325.

Zielhuis, R. L., del Castilho, P., Herber, R. F. M., and Wibowo, A. A. E. 1978. Levels of lead and other metals in human blood: Suggestive relationships, determining factors. *Environ. Health Perspect.* 25: 103-109.

*Received June 29, 1983*
*Accepted January 15, 1984*

ATTACHMENT D-1

A Review of the Memorandum Entitled, "*Manganese in Gasoline, Toxicity Problems*" by the Director, NIEHS dated June 7, 1990

Carl O. Schulz, Ph.D., DABT

In his memorandum, dated June 7, 1990, the Director of NIEHS expressed concern regarding the proposed use of manganese-containing compounds as additives in gasoline. The memorandum presents reasons for that concern. The questions raised show misunderstanding of the chemical and biological properties and behavior of manganese and its compounds and do not reflect the large body of scientific information on manganese.

In paragraph 1, the concern is raised that manganese is toxicologically similar to lead. This is not scientifically supportable and is addressed in more detail in a separate document. The Director also indicates concerns regarding organic and inorganic forms of manganese. Since the available data indicate that there are no organic compounds of manganese present in the exhaust from engines fueled with gasoline containing MMT (manganese is emitted as manganese oxides with $Mn_3O_4$ predominating [Ter Haar et al. 1975] - JAPCA 25:858-860), this proceeding addresses only the potential hazards to human health of inorganic forms of manganese.

In paragraph 2 the Director speculates, without evidence, that MMT is readily absorbed "via the nose" and that this might result in higher levels of manganese in the CNS than comparable doses by other routes. As stated above, the manganese is emitted in engine exhaust as inorganic oxides, mostly presumably in particulate form. Depending on particle size, a significant but unknown proportion of the manganese that enters the respiratory tract will deposit on the surface of the upper respiratory tract and will be expelled or cleared to the gastrointestinal tract by normal mucociliary clearance mechanisms. There is no evidence, and it is unlikely, that a significant amount of manganese will be absorbed through the mucosa of the nasopharyngheal region of

the upper airway. In any event, this does not guarantee ready access to the brain. Absorption would occur into the general circulation and the blood supplying the capillary bed of the nasopharyngheal mucosa must pass back through the heart, lungs, and probably the kidneys and liver before it reaches the brain. There is no shortcut from the nose to the brain as implied in this paragraph.

The Director points out that most of the toxicity data are by the oral route of administration and do not apply to other routes. This generalization applies only to experimental studies. There is a large body of health effects information derived from studies of workers who are occupationally exposed to manganese compounds almost exclusively by the inhalation route (see HEI 1988, Cooper 1984, EPA 1984, and WHO 1981 for reviews of these studies).

In paragraph 3 the Director asserts that the effects of manganese on the central nervous system are not reversible "easily, if at all". However, the World Health Organization concluded that the neurological damage attributable to manganese exposure is reversible if the patient is removed from exposure at an early stage and that the symptoms of manganism can be treated by administration of L-Dopa (WHO 1981).

In paragraph 5 the Director states that $Mn_3O_4$ is much more toxic than MnO. While no documentation is provided for this assertion, it is probably based on the acute oral toxicities of these compounds in laboratory animals. The relevance of acute toxicity to the relative human health hazards of these two forms of manganese resulting from chronic exposure to low concentrations in ambient air is doubtful. Moreover, because, as stated above, the toxicity of MMT is not at issue here, the relative toxicity of MMT and tetraethyl lead is irrelevant.

The point of paragraph 6 is not apparent. Epidemiologic studies are incapable of detecting low incidences of subtle adverse health effects because of the lack of statistical power. Ordinarily such studies are conducted in relatively small cohorts of highly exposed individuals in order to maximize the probability of a statistically significant outcome. It is asking

too much of epidemiologic methods to rely on such studies to provide quantitative dose-response data within the range of expected environmental exposures.

The argument raised in paragraph 7 is purely speculative and once again raises the issue of toxicological parallels between manganese and lead. These issues are dealt with in a separate memorandum.

In conclusion, the memorandum from the Director of NIEHS fails to provide a scientific basis for any of the concerns raised therein regarding inorganic forms of manganese, and does not provide a basis for rejecting the data on which Ethyl Corporation bases its request for approval of a manganese additive in gasoline.

ATTACHMENT D-2

*Contrasting Public Health Concerns Raised by Lead, Manganese, and MMT*

By Carl O. Schulz, Ph.D., DABT

In the memorandum from the Director of NIEHS it is implied that manganese and lead are similar elements presenting similar public health problems. Moreover, this memorandum and the letter from Dr. Needleman imply that organic compounds of Mn and Pb have similar toxicities. The only characteristics shared by lead and manganese are that they are metals, form compounds in which they exist in the +2 and +4 oxidation states, and may adversely affect the central nervous system under certain conditions. The differences between them chemically, biologically, and environmentally are many and profound.

Chemically, lead is a "heavy" metal, atomic weight 207, in group IVA of the periodic table. Manganese on the other hand is a "light" metal, atomic weight 55, in transition group IIIA. The chemical behavior of manganese resembles that of its fellow transition metals chromium and iron much more than lead. (Pauling 1964). There are 11 valence states of manganese, 8 of which are oxidation states. The most stable of these (+2 and +3) occur in the environment; only the +2 oxidation state of lead is common in naturally occurring compounds. (Grayson, 1985, pp. 728-730).

Environmentally, manganese is the twelfth most abundant element in the earth's crust and is present in soil, water, and in all plant and animal tissues. (Cooper, 1984). Humans are exposed to relatively high concentrations of manganese in food, water and air even in the absence of pollution. (WHO, 1981). Lead, on the other hand, is present in the earth's crust at concentrations 1 to 2 orders of magnitude below those of manganese (IARC, 1980), and in the absence of anthropogenic sources of lead pollution is present only at low levels in the human environment.

Biologically, the differences between lead and manganese are even more striking. Manganese is an essential trace element in human and animal nutrition. (NAS, 1973; WHO, 1981). Lead has no known beneficial role in biological systems. (Goyer, 1986). Homeostatic mechanisms appear to regulate the uptake and excretion of manganese in higher animals such that individuals having widely different intakes of this element have similar body burdens. (HEI, 1988; Cooper, 1984). There are no known mechanisms that regulate the uptake of lead. Manganese is readily excreted from the body in a biphasic manner. (WHO, 1981). The "slow" phase has a half life on the order of 38 days. Although there is some evidence that manganese levels in the brain decrease at a slower rate than those in the rest of the body, there is no evidence that manganese accumulates in the brain at "normal" environmental exposures. While some lead is eliminated from the body rapidly, much of the lead to which humans are exposed is sequestered in bone, where it has a half-life of more than 20 years, and other tissues, from which it is eliminated very slowly, if at all. (Goyer, 1986). Lead affects the peripheral and central nervous systems. While the mechanism is not clearly understood, it is clear that the function of the nervous system in its entirety is involved. Manganese, on the other hand, appears to affect the extrapyramidal motor system in the basal ganglia in the central nervous system, possibly through interference with dopamine metabolism. (HEI, 1988; Bleecker, 1988). The concentrations required for this to occur appear to be far above "normal" concentrations and the effects may be modulated or eliminated by the administration of dopamine precursors. Limited evidence indicates that the central nervous system effects of manganese are reversible, at least in the early stages of intoxication. The absence of neurological impairment associated with normal environmental exposures to manganese, the limited evidence for reversibility, and the effective treatment of early symptoms with therapeutic agents support the possible existence of a threshold for the neurological toxicity of manganese. No threshold has as yet been established for the toxic effects of lead on the central nervous system.

Pauling, L. 1964. College Chemistry. 3rd Ed. W.H. Freeman & Co., San Francisco. Pp. 623, 693-697.

Goyer, R.A. 1986. *Toxic effects of metals in Klaassen, C.D.*, Amdur, M.O. and Doull, J. (eds.), Casarett and Doull's Toxicology: The Basic Science of Poisons. 3rd Ed. Macmillan Publishing Co., New York. Chapter 20, pp. 582-635.

International Agency for Research on Cancer (IARC) 1980. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Metals and Metallic Compounds. Vol. 23. IARC, Lyon, France. Pp. 325-415.

ATTACHMENT D-3

A Brief Comment on *"Manganese and Human Health"* by John Donaldson in Manganese in the Canadian Environment by the National Research Council Canada, 1988

Carl O. Schulz, Ph.D.

This document is neither a research article nor an objective scientific review article. It is an extended essay in which the author lets his imagination run free, citing mere wisps of scientific evidence in support of a grandiose hypothetical scheme of manganese toxicity. It is fair to say that the only type of peer-reviewed scientific journal that would publish such a speculative piece would be a journal devoted to scientific hypotheses. As support for the hypothetical nature of the document one has only to analyze the language as follows:

| Page | Phrases (emphasis added) |
|---|---|
| 90 | "and may be therapeutically useful..." |
| | "consideration should be given to the..." |
| | "Possible sites may be free carboxyl..." |
| 91 | "may have considerable relevance towards..." |
| | "seems to indicate that environmental..." |
| | "may play a previously unsuspected..." |
| | "manganese may contribute..." |
| | "which may not completely manifest itself..." |
| 92 | "it is considered by some investigators that..." |
| | "and possibly some other neurodegenerative..." |
| | "manganese may induce initial sub-clinical..." |

93 "Calne et al. 1986) have suggested that..."
"they have extended this hypothesis to..."
"The practical implications of this intriguing hypothesis strongly suggest that..."
"A prime candidate for examination in causal mechanisms linking..."

94 "Certainly the possibility of initial..."
"it should be possible to determine..."

This type of analysis throughout the document reveals the purely speculative nature of the author's arguments. However, the author writes his own bottom line on page 92.

> "Whether manganese can in fact induce an [sic] lesion in discrete and vulnerable compartments of the CNS during the early years and which does not result in neurotoxicity until later stages of development is presently unknown. However, because manganese is an important neurotoxin whose precise mode of nervous tissue and behavioral toxicity is still unknown, it should be considered a prime candidate in studies set up to examine this specific question. Also, the concept that manganese may induce initial sub-clinical neuronal damage which remains dormant for decades until late life when as a result of potentiated senescence changes, it results in a chronic neurologic disorder such as Parkinson's disease, Alzheimer's disease, or amyotrophic lateral sclerosis (ALS) has not yet been adequately addressed." (Emphasis added)

One wonders why the author did not also include a number of other neurological diseases of unknown etiology, e.g. multiple sclerosis and muscular dystrophy, on his list of disorders attributable to manganese. The evidence that he cites in support of an etiologic link between manganese exposure and various neurologic disorders is of the weakest type consisting almost entirely of case reports and ecological studies. It is of

interest also, that the author does not address the fact that while the symptoms of chronic manganese intoxication mimic those of Parkinson's disease, the brain lesion characteristic of manganism can be distinguished from that of Parkinson's disease (Mena et al. 1967; Cooper 1984; and USEPA 1984) [as cited in the HEI 1988 report].

ATTACHMENT D-4

# Review of Testimony by Ellen Silbergeld

By Carl O. Schulz, Ph.D., DABT

Dr. Silbergeld testified on behalf of the Environmental Defense Fund (EDF) in opposition to the use of MMT as a gasoline additive. The essence of her opposition was that adding manganese to gasoline is analogous to adding lead to gasoline. This argument is flawed on chemical, biological, and environmental grounds as stated earlier. Dr. Silbergeld cited a study by Davis et al. (1988) as indicating that the use of manganese in gasoline causes an increase in airborne manganese. She failed to indicate that only in a congested urban center did vehicular sources contribute significantly to airborne manganese concentrations and the average contribution of suspended soil exceeded the average vehicular contribution in all locations.

Dr. Silbergeld asserted that "both lead and manganese are elements and as such will not degrade or quickly disappear from stable environmental compartments..." The same can be said about iron, yet no one would assert that iron is like lead. In fact, manganese resembles iron much more closely than lead in that both are transition metals, are abundant in the earth's crust, are essential to human health, and their absorption and excretion are controlled by homeostatic mechanisms. None of these is true for lead.

Dr. Silbergeld asserted, without evidence, that manganese is a cumulative toxin in that both its absorption and retention as well as its toxicity increase with time. Toxicity is an inherent characteristic of a chemical and does not change "with time". With regard to absorption and retention, the EPA concluded in a document for which Dr. Silbergeld was a peer reviewer that "Manganese metabolism is rigorously controlled by homeostatic mechanisms. . . . . The absorption, retention, and excretion of manganese are interrelated and respond very efficiently to an increase in manganese concentration." (USEPA 1984).

Dr. Silbergeld asserted that there are no data on the low-level chronic sequelae of manganese exposure. This statement ignores the fact that humans are continually exposed to relatively high levels of manganese in food and water, and that manganese is an essential element in human nutrition.

Her statement that manganese may accelerate normal cell loss during senescence is a restatement of a speculative hypothesis advanced by John Donaldson and does not recognize the pathological differences between manganese neurotoxicity and other neurological disorders associated with disease and/or aging (see Bleecker 1988).